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DIET AND TISSUE GROWTH

VII. RESPONSE TO HIGH PROTEIN DIETS AND UNILATERAL NEPHRECTOMY DURING REPRODUCTION AND LACTATION IN THE RAT, WITH PARTICULAR REFERENCE TO KIDNEY CHANGES IN BOTH MOTHER AND OFFSPRING *

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The possible relationship of dietary protein to changes in renal function or renal structure has received increasing attention during the past few years. A review by Mitchell [1] indicates the disagreement that still exists not only concerning the production of any change by increased protein intake, but also concerning the nature of the observed changes. Mitchell brought out also the difficulty of harmonizing the results of different investigators, because of the lack of uniformity in the experimental conditions imposed and the inherent complexity of the variables. There seems to be justification for the recent trend toward study of special aspects of the problem, since more general methods of approach have led to seemingly contradictory conclusions. It is possible that only by observing the physiologic response of animals under widely varying but carefully controlled experimental conditions can the factors

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1. Mitchell, H. H.: J. Nutrition **1**:271, 1929.

be demonstrated which contribute to the renal changes caused by certain diets. The types of observations made may also be extended to advantage. For instance, comparatively few detailed studies of blood constitutents have accompanied investigations of renal changes.

It was from such standpoints that the present research was undertaken. Several methods have been utilized for the intensification of the physiologic task of excretion. In the first place, advantage has been taken of the demonstrated influence of unilateral nephrectomy on renal injury and on the compensatory enlargement of the remaining kidney during a high protein régime (Smith and Moise [2]). In addition, the functional stress has been augmented through an increase in the nutritional needs and metabolism of the animal by the introduction of gestation and lactation, factors that have been used by MacKay, MacKay and Addis [3] and MacKay [4] in connection with studies involving a comparatively low protein intake. The rat was chosen as the experimental animal in the present research because of the extensive comparative data available for this species. The scope of the research has been amplified by an extensive study of the fluctuations in one constitutent of the blood, namely urea, the results of which will be reported in a succeeding paper.

EXPERIMENTAL METHODS

Plan of Experiment.—Unilateral nephrectomy or laparotomy alone was performed on animals, which were immediately placed on rations containing varying concentrations of protein; the rats were bred as soon as possible thereafter. When the young were born, the number in the litter was reduced to eight. The litters were weaned on the twenty-first day or, in certain cases in which data on the kidneys of the young were desired, on the seventeenth day. The mothers were either killed when the young were weaned or were remated. In some of the control experiments, females were killed at the time the litters were expected to be born or just after the birth of the litter; and in certain others, the animals were not mated. The remaining left kidneys were removed together with the hearts at autopsy for study.

Selection and Care of the Animals.—The albino rat (*Mus norvegicus-albinus*) was used. For the preliminary part of the investigation, the rats were obtained from the colony of the Laboratory of Physiological Chemistry and from the (Osborne and Mendel) colony at the Connecticut Agricultural Experiment Station; later, from a second generation bred from the latter stock in the Laboratory of Physiological Chemistry. The unusual vigor of these animals, their capacity for growth and the high standard of uniformity procured by years of selection and feeding are significant elements of success for this type of experimentation. The rats were used only after they had reached adult weight, for the reason that it was desirable to eliminate as far as possible increase in kidney size due to normal growth of the animal itself.

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2. Smith, A. H., and Moise, T. S.: J. Exper. Med. **45**:263, 1927.

3. MacKay, L. L.; MacKay, E. M., and Addis, T.: Proc. Soc. Exper. Biol. & Med. **22**:536, 1925.

4. MacKay, L. L.: Am. J. Physiol. **86**:215, 1928.

The rats were kept in individual cylindric cages with wire mesh bottoms which stood high enough above a layer of shavings so that there was no possibility of any consumption of this material by the rats. Bedding in the form of paper crepe was provided for the mother rats the day before the litters were expected to be born. Water was supplied from a device with a large capacity in order to insure an adequate source at all times; for the unusually large water intake of these animals under the experimental conditions employed rendered this precaution necessary.

The Rations.—Rations were devised to make as striking contrasts as possible in the concentration of protein in the diet. It was necessary, however, to avoid endangering success in lactation by too low a protein intake, on the one hand,

TABLE 1.—*Composition of Rations*

Components	Concentrations of Components in Various Diets											
	1	2*	3	4	5	6a*	6b	7	8	9	10	11
Protein, per cent	70	67	74	70	68	67	70	41	16	21	21	22
Crude casein (including irradiated), per cent	86	76	..	..	72	80.4	..	50	20	20	20	..
(Crude casein irradiated†), per cent	(20)	..	..	..	..	..	..	(20)	(20)	..	..	..
Cooked egg albumin, per cent	..	..	86	76	..	..	80.4	..	..	..	..	20
Wheat embryo, per cent	..	20	..	20	20	5	..	..	..	20	20	20
Cooked starch, per cent	..	..	..	..	..	..	..	36	66	56	54.3	56
Salt mixture, per cent (Osborne and Mendel: J. Biol. Chem. **37**: 572, 1919)	4	4	4	4	4	4	4	4	4	4	4	4
Added calcium carbonate, per cent	..	..	..	..	4	0.64	0.64	..	..	..	1.67	..
Butter fat, per cent	10	..	10	..	..	10	10	10	10	..	..	..
Daily additions to basal rations												
Lettuce,¶ Gm.	15	..	15	..	..	15	15	15	15	..	..	..
Yeast,† Gm.	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3
Cod liver oil,† cc.	..	0.3-1.5	..	0.3-1.5	0.3-1.5	0.3-1.5	0.3-1.5	..	..	0.3-1.5	0.3-1.5	0.3-1.5

* Additions of a potent alcoholic extract of wheat embryo, of "marmite" (a commercial yeast product supplied by Dr. Katharine Coward, London), of a tested lot of Harris' yeast concentrate (lot no. 1030, assayed in this laboratory and found to be potent) and of a commercial wheat germ oil were fed to certain rats on rations 2 and 6a.

† Variations in these ingredients were introduced as follows:

Irradiated foods: Before Oct. 16, 1927, additions of vitamin D were made to the basal ration by means of irradiating a portion of the casein of certain diets (20 Gm. per hundred grams of ration being so treated). After this date, 50 mg. of irradiated yeast was incorporated in each gram of yeast fed in the ration, instead of irradiated casein.

Amounts of yeast: Before parturition, the animals had 1 Gm. per day; during the first and second weeks of lactation, 2 Gm., and during the third week of lactation, 3 Gm.

Cod liver oil: Up to Nov. 14, 1927, 0.3 cc. was fed daily. Between Nov. 14, 1927, and Dec. 10, 1927, 0.5 cc. was fed daily during the interval up to parturition, 1 cc. during the second week of lactation and 1.5 cc. during the third week of lactation. After Dec. 10, 1927, 0.5 cc. was fed daily during the interval up to the occurrence of the placental sign, and 1.5 cc. during the interval between the occurrence of the placental sign and the weaning of the young.

¶ Analysis of lettuce (bought in New Haven) by personal communication to the authors by Dr. A. J. Wakeman, Connecticut Agricultural Experiment Station: Water content, 93.6 per cent (average of analyses on 7 samples); ash content on moisture-free lettuce, 22.5 per cent (average of analyses on 2 samples).

and by such an excess of protein, on the other, that too small an amount of food substances carrying the necessary vitamins would be included in the ration. Table 1 presents the composition of the various food mixtures.

The composition of ration 1 was arranged to approximate closely the mixture fed extensively by Smith and Moise,[2] but was abandoned later because trial proved that reproduction on it was relatively unsuccessful. Rations 2, 4, 5, 6a, 9, 10 and 11 introduced wheat embryo and cod liver oil as carriers of an additional vitamin supply. In rations 3, 4, 6b and 11, cooked egg albumin was substituted for casein in corresponding rations for the purpose of avoiding the high content of phosphorus supplied by the casein, since an influence of phosphorus on renal enlargement had

been suggested (MacKay, MacKay and Addis [5]), although this was questioned by others (Osborne, Mendel, Park and Winternitz [6]). In ration 5 also, the high ratio of phosphorus to calcium was changed to one in which calcium was in twice as great concentration by weight as phosphorus (a ratio suggested as optimum by Dr. A. T. Shohl) by the addition of appropriate amounts of calcium carbonate to the casein ration and to the yeast added apart from the rest of the food. Table 1 also lists certain substances as carriers of the vitamins B and G, in addition to the yeast supplied. These were used in the case of a few rats to insure an adequate supply of vitamin B "complex" if necessary to meet the requirements of animals on high protein levels, as Hartwell [7] suggested that the need for this "complex" is augmented by high protein intake. She estimated that every 20 Gm. of casein in

TABLE 2.—*Previous Rations of Rats Used in Experiments*

Rats from Osborne and Mendel Laboratory at Connecticut Agricultural Experiment Station*	
6, 8, 16, 19, 20, 22, 23, 29, 30, 31, 34, 35, 36, 69, 70, 71, 72, 73, 74, 80, 81, 82	**Ration 1** Casein ..... 30 per cent Salt mixture ..... 4 per cent Starch ..... 22 per cent Butter fat ..... 9 per cent Lard ..... 15 per cent Wheat germ ..... 20 per cent
76, 77	**Ration 2** Same as ration 1 plus daily additions of Yeast ..... 0.2 Gm. Lettuce ..... 30.0 Gm.
78, 95	**Ration 3** Same as ration 1 plus daily addition of Yeast ..... 0.2 Gm.
79, 96	**Ration 4** Same as ration 1 plus daily additions of Yeast ..... 0.2 Gm. Lettuce ..... 40.0 Gm.
88, 89, 90, 91, 92, 93, 94	Dog biscuit and green food
Rats 61 to 68, inclusive, were virgin females from the stock of this laboratory	**Stock Ration** (Modified Sherman Ration) Whole dried milk ..... 32.5 per cent Ground whole wheat ..... 65.5 per cent Sodium chloride ..... 1.0 per cent Calcium carbonate ..... 1.0 per cent Lettuce ..... 5 or 6 times, wk.
Rate 97 to 165, inclusive, the second generation from the stock of the Connecticut Agricultural Experiment Station, were virgin females when used for the present experiment	Modified Sherman ration

* These rats produced one or more litters on the rations listed before being used for the present experiment.

the mother's diet required from 6 to 8 Gm. of "marmite" (a commercial yeast preparation) for the rearing of suckling young (Hartwell [8]). Reader and Drummond [9] secured normal rates of growth and freedom from renal damage or hypertrophy on high casein rations by increasing the proportion of "marmite" fed,

5. MacKay, L. L.; MacKay, E. M., and Addis, T.: Proc. Soc. Exper. Biol. & Med. **24**:130, 1926.

6. Osborne, T. B.; Mendel, L. B.; Park, E. A., and Winternitz, M. C.: J. Biol. Chem. **71**:317, 1927.

7. Hartwell, G. A.: Biochem. J. **18**:785, 1924.

8. Hartwell, G. A.: Biochem. J. **19**:1075, 1925.

9. Reader, V., and Drummond, J. C.: Biochem. J. **20**:653, 1927.

until the ratio of protein to this yeast extract had a value of 5 or less. Hassan and Drummond[10] reported that the factor in yeast concerned with rendering high protein diets adequate for growth seemed to be the one resistant to heat and alkali. The wheat germ oil was added in certain cases because of the suggestion of Evans and Burr[11] that a relative lack of vitamin E might be a cause of failure in suckling young on certain diets. Ration 8 carries the lowest level of protein assumed to possess a safe margin for entirely successful reproduction and rearing of young. Ration 7 was planned to replace ration 1 in case no reproduction could be secured on the higher level.

The casein employed was a washed crude product. Dried, commercial egg albumin was dissolved in a small amount of distilled water, poured into boiling distilled water and thoroughly coagulated, with additions of glacial acetic acid to make the mixture slightly acid to litmus. The entire mass was dried without separation of the liquid from the solid portions. Starch was converted to a translucent paste by heating in water. Both the cooked egg albumin and starch after drying were ground finely and incorporated in the basal rations in this form. Butter fat, free from water, was filtered through filter paper in a hot water funnel.

The alcoholic extract of wheat embryo was prepared according to the method of Sure.[12] Each kilogram of wheat embryo was percolated with 5 liters of 75 per cent ethyl alcohol at room temperature, and, after being filtered, the alcohol was evaporated in vacuo. The preparation was fed as a water solution made up to known volume. Its potency was assayed, and growth was obtained with as small a daily portion of this extract as the equivalent of 2 Gm. of wheat embryo.

Yeast and casein, in 100 Gm. lots, were each spread on pans 20 by 20 inches (50.8 by 50.8 cm.) and irradiated for half an hour under a mercury vapor quartz lamp using 4 amperes and 110 volts, direct current, at a distance of 2 feet. Each lot was stirred once at the end of fifteen minutes.

Methods of Analysis.—Calcium was determined by the Tisdall and Kramer method (Tisdall[13]), as modified by Clark and Collip.[14]

Phosphorus was determined by the method of Bang as described by Greenwald[15] and modified by Shohl and Bennett.[16]

Urinary albumin was determined by the method employed by Smith and Moise.[17]

Surgical Technic.—The procedure of Smith and Moise[2] was followed in performing unilateral nephrectomy. Laparotomy alone was performed on some of the animals (rats 108, 112, 116, 120, 124, 128, 132 and 135) as a control experiment to test the part which an operative procedure might play in any possible effects of nephrectomy. The laparotomy included the anesthesia and incisions described by Smith and Moise,[2] together with a careful lifting of the kidney and a somewhat less extensive dissection of the surrounding fat.

Removal and Fixation of Kidney at Autopsy.—As much of the adjacent fat as possible was cut away from the kidney with sharp pointed scissors, but the capsule

10. Hassan, A., and Drummond, J. C.: Biochem. J. **21**:653, 1927.
11. Evans, H. M., and Burr, G. O.: J. Biol. Chem. **76**:273, 1928.
12. Sure, B.: J. Biol. Chem. **74**:55, 1927.
13. Tisdall, F. F.: J. Biol. Chem. **56**:439, 1923.
14. Clark, E. P., and Collip, J. B.: J. Biol. Chem. **63**:461, 1925.
15. Greenwald, I., and Gross, J.: J. Biol. Chem. **66**:185, 1925.
16. Shohl, A. T., and Bennett, H. B.: J. Biol. Chem. **74**:247, 1927.
17. Smith, A. H., and Moise, T. S.: J. Exper. Med. **46**:27, 1927.

was not removed. In case of the right kidney, this dissection was carried out on a glass plate, and the kidney removed at once to a weighing flask and covered. However, in the case of left kidneys in which considerable hypertrophy had taken place, it was found that so much urine was held in the hilus of the kidney that it was necessary to absorb this with filter paper. Even in cases of hydronephrosis, this was found to be an effective method of removing the excess of urine, since on making a longitudinal section little of this fluid was visible. The two halves of the kidney were fixed for from three to eight days in a 10 per cent formaldehyde solution before being embedded and sectioned. Eosin and hematoxylin were used as stains. The method followed in the excision of the heart was to lift it by its apex with mouse tooth forceps and make a transverse incision through the blood vessels as close to the auricles as possible. The stub of the aorta was trimmed when necessary to a short uniform length. An incision was made into the auricles and ventricles, so that any clotted blood might be removed.

Calculation of Renal Enlargement.—The method of Smith and Moise [2] was used in calculating the percentage of renal enlargement based on body weight. An example of the calculation based on heart weight is given in table 3.

Use of Vaginal Smears.—In those of the present experiments which involved reproduction, observation of vaginal conditions by means of the technic of Long

TABLE 3.—*Calculation of Per Cent of Renal Enlargement Based on Heart Weight*

	Weight of Heart at Autopsy, Gm.	Weight of Left Kidney at Autopsy, Gm.
Rat 77	0.741	2.504
Donaldson's nearest corresponding values	0.734 0.744	0.775 0.787
Donaldson's values by interpolation	0.741	0.784
Difference (enlargement)	2.504 − 0.784 = 1.720 Gm.	
Degree of enlargement, $\frac{1.720}{0.784} \times 100 = 219.4$ per cent		

and Evans [18] proved of advantage in establishing the time of reappearance of the regular estrous cycle after operation, selecting a time for mating, detecting insemination and obtaining evidence of implantation.

The technic of the vaginal smear was adapted to the needs of the problem. A plentiful number of cells in a smear could be easily obtained if a blunt syringe made from glass tubing and rubber bulb were substituted for the small glass spatula ordinarily used, and a small amount of physiologic solution of sodium chloride was injected into and then withdrawn from the vagina.[19]

RESULTS

Effects of a Diet Rich in Protein on Ovulation and Gestation.—A valuable index of physiologic well-being was discovered by Long and Evans [18] through the use of the vaginal smear technic. They observed a regular tendency to the prolongation of the time interval of the estrous

18. Long, J. A., and Evans, H. M.: Memoirs of the University of California, Berkeley, University of California Press, 1922.

19. Dr. Myra Sampson of Smith College suggested this procedure.

cycle in all cases of undernutrition and concluded therefrom that a regular cycle of from three to five days is a more sensitive index to the well-being of young adult female rats than bodily activity, glossy hair, normal weight or other recognized signs of health.

In the present experiments, as might be expected, the estrous cycle was somewhat disturbed for a shorter or longer interval following the operation of unilateral nephrectomy, but when it became established again it was of interest to note that with the exception of the rats fed egg albumin the regular interval was four or five days in length. This observation therefore furnishes evidence of physiologic well-being in the rats fed high casein diets after the removal of one kidney.

No toxic signs were observed during gestation in any of the animals.[20] Determinations of the albumin in a two or three days' collection of urine were made in the case of ten of the animals for the period immediately preceding parturition. These determinations revealed only the traces of albumin normally found in the urine of the rat. Albuminuria occurs so frequently in cases of human pregnancy that a failure to find significant increases here is of interest.

The weight of the young was regularly noted the day after the litter was born, so that the mother rat should not be disturbed during the first hours after parturition. This procedure did not give a true birth weight, but the latter was not obtainable in many cases in any event, since birth occurred frequently during the night, and the young had already sucked when they were found in the morning. Therefore, the records of "birth weight" in this investigation represent the weight of the young at an age of from 1½ to something less than 1 day plus an increment in weight of a variable amount of milk. The reliability of the figures given so frequently in the literature on the birth weight of young on given diets is open to question. Only with some technic such as that which Long and Evans [18] described for removing the young at birth can adequate figures be obtained, free from the objections offered. Since the same variables apply to the young of mothers on all diets, a comparison has been made in table 4 of the average weight of the newly born young on the various rations. It will be seen from table 4 that the average weights of the baby rats 1 day old born from mothers on these various rations do not differ strikingly. The highest average weight occurred on a low protein ration, containing

20. There were two instances of abnormally prolonged parturition with the greatly oversized young born dead. In one of the cases, the female gave birth to a normal second litter. In the other, mating was not attempted again, and the animal was killed for the examination of the tissues. Diet was probably not responsible for the abnormal condition, since one of the females received a low protein ration and the other a diet rich in protein. The condition may have been associated with the occurrence of a first pregnancy at a relatively advanced age.

21 per cent, but not on the lowest, containing 16 per cent. The factor of nephrectomy seemed to have no influence on birth weight (ration 2).

Effects on Lactation.—That certain abnormalities of diet may be most clearly elicited by the demands of lactation has been frequently pointed out. The efficiency of milk production on an adequate diet is evidenced in a number of ways. The flow of milk begins promptly at parturition. The abundance of the supply can easily be judged by the distention of the abdomen of the baby rats and by the appearance of the full stomach as a white spot of varying size viewed through the semitransparent abdominal walls. Well-fed baby rats sleep a great deal of the time, not nursing excessively but appearing satisfied. The hair shows as a tinge of white at the end of one week. At this time, the body has more than doubled in weight. At about 2 weeks of age, the eyes are open, and a distinct covering of hair has formed. The body weight is more than trebled. The body looks plump. The back

TABLE 4.—*Average Weights of Young Approximately One Day of Age Born from Mothers on Rations Containing Different Concentrations of Protein*

Condition of Mother Rat	Average Weight of Newly Born Young, Gm.	Ration	Amount of Protein in Diet, %
Nephrectomized	5.1	1	70
Nephrectomized	5.7	2	67
Intact	5.7	2	67
Nephrectomized	5.6	5	63
Nephrectomized	5.7	6a	67
Nephrectomized	5.7	7	41
Nephrectomized	5.4	8	16
Nephrectomized	6.5	9	21
Nephrectomized	5.6	10	21

especially at the hips is noticeably broad, and the whole body looks well proportioned. The skin is loose, but has subcutaneous fat, so that it is not drawn into thin, wrinkled folds. At about the sixteenth or seventeenth day, the young are wandering freely about the cage and are frequently found in the mother's food cup; nibbling of her ration begins some time before the twenty-first day. The hair at this time is luxurious and smooth and neither "stands on end" nor looks greasy and sticky. The mother rat usually maintains her weight during lactation.

Although a study of the possible effects of high protein diets on lactation was incidental to the general problem, a comparison of the results summarized in table 5 is of interest.

The records of the rats on rations 1, 7 and 8 carrying 70, 41 and 16 per cent, respectively, of protein derived from casein make it clear that reproduction and lactation may be relatively unsuccessful on certain rations that are very rich in protein and that include amounts

of vitamin-containing foods approximately adequate when incorporated in control rations of lower protein content. The same amount of salt mixture was added to each of the three rations, hence the only important variable in the content of inorganic material was in the different amounts of phosphorus and calcium introduced into the diet with the crude casein. In the experiments of Maynard and Bender,[21] the salt concentration of both the high protein and the low protein rations was made identical by adding appropriate amounts of calcium and phosphorus, as well as the usual salt mixture to the ration with the lower protein. This was not done in the present experiment, although enough calcium was added to one of the high protein rations (5) to make the

TABLE 5.—*Reproduction and Lactation Records of Rats, on the Various Rations Listed in Table 1*

Ration	Females on Ration	Condition of Female Rats	Females Failing to Breed, %	Number of Litters	Total Young Born on Ration	Total* Young Living After One Day	Young Living on 21st Day, %†	Average Weight of Young on 21st Day, Gm.	Main Source of Protein in Diet	Amount of Protein in Ration, %
1	12	Nephrectomized	25	9	61	55	47.3	22	Casein	70
7	8	Nephrectomized	37.5	5	41	40	78.4	33.3	Casein	41
8	5	Nephrectomized	20	4	36	29	100.0	33.0	Casein	16
2	33¶	Nephrectomized	21.1	40	300	272	74.7	28.1	Casein	67
2	9	Intact	33.3	6	42	37	73.0	27.3	Casein	67
5	8	Nephrectomized	37.5	5	36	27	85.2	28.8	Casein	63
9	3	Nephrectomized	00.0	3	27	24	91.0	33.4	Casein	21
10	10	Nephrectomized	20.0	9	63	62	76.9	36.3	Casein	21
4	4	Nephrectomized	75.0	1	6	6	00.0	....	Egg albumin	70
3	6	Nephrectomized	83.3	1	8	8	37.5‡	9.7	Egg albumin	74
6b	3	Nephrectomized	33.3	2	13	12	58.3	12.9	Egg albumin	70
11	2	Nephrectomized	50.0	1	7	7	100.0	15.7	Egg albumin	22
6a	4	Nephrectomized	00.0	4	34	31	45.1	29.7	Casein	67

* Any differences between the totals in this column and the preceding column may be due either to a reduction of the litter to a total of eight, a practice applied to all litters of more than eight young, or to mortality of the young or both.

† The percentage is based on the number living after one day (see preceding column).

¶ Twenty more nephrectomized females listed in other tables on this diet are not included here, because part of them were killed when the litters were about to be born, and the young of part of them were killed for autopsy records on the seventeenth day of nursing instead of the twenty-first.

‡ Three of the young were kept alive by being fed a solution of cane sugar three times daily with a syringe, starting on the fourteenth day of lactation.

ratio of calcium to phosphorus 2 to 1, a proportion considered optimal by Shohl. Maynard and Bender[21] concluded that there was no appreciable difference in the effect on reproduction of their high protein and low protein diets; but it is to be noted in their experiments that lactation was somewhat superior on the lower concentration of protein, 82.2 per cent of the young living to the 20th day and weighing 32.2 Gm. on 18 per cent of protein, whereas 80.2 per cent of the young lived on 50 per cent of protein and weighed 28.7 Gm. It should also be noted that the concentration of protein in their "high protein" ration (50 per cent) approximates much more closely the 41 per cent protein

21. Maynard, L. A., and Bender, R. C.: Proc. Soc. Exper. Biol. & Med. **25:** 388, 1928.

of ration 7, grouped here as one of the rations with lower protein content, than it does the 70 per cent of ration 5 used in these experiments as the high protein type. The young on both rations 7 and 8 averaged approximately 33 Gm. at 21 days of age, a record fairly comparable with Maynard and Bender's results. The chief difference noted between rations 7 and 8 was in the mortality of the young. The contrast of litters on these two rations with litters born on ration 1 is much more striking.

That additions of yeast, cod liver oil and wheat embryo improved the records made by the animals on high protein ration 1 is indicated by the response to ration 2, in which these additions are included, although here also the performance falls short of that on the corresponding low protein ration 9 to which the same additions have been made. On ration 2, the fact is also established that reproduction and lactation are fully as good in the partially nephrectomized as in the intact animals. This lends validity to comparisons of the results on the animals with one kidney herein obtained with the results of other laboratories on intact animals. The adding of calcium to rations 2 and 9, in rations 5 and 10, respectively, to bring up the ratio of calcium to phosphorus to a 2:1 proportion, made no consistent improvement in the records of rats on either the high protein or the low protein ration. The largest young of the series were produced on ration 10, but reproduction and survival of the young were not so good as on ration 9.

The detrimental effects on reproduction and lactation of the introduction of cooked egg albumin in place of casein in the high protein rations is seen in the records of rats on rations 3, 4, 6b and 11. The reason for this condition demands further investigation.

The averages on ration 6a (table 1) represent a few animals to the rations of which were added high concentrations of vitamin E and of vitamin B "complex," particularly the antineuritic vitamin B, since Evans and Burr [22] have shown that crude casein itself contains vitamin G. As no noteworthy improvement resulted from either addition, fuller details need not be presented. The results of a more crucial experiment are presented in table 6. Several litters were divided as fairly as possible into two groups each. One group was used as a control; the other was given doses of wheat germ oil, "marmite," Harris' yeast concentrate or alcoholic extract of wheat embryo daily from a glass syringe tipped with fine rubber tubing. Quantitative records of intake could not be secured,[23] but it appeared evident that each rat consumed liberal amounts of the supplemental food. Although at the end

22. Evans, H. M., and Burr, G. O.: J. Biol. Chem. **76**:263, 1928.

23. Some of the liquid that had been placed in the mouths of the young rats sometimes ran out and was lost in spite of the utmost care in feeding.

of the feeding period the two groups sometimes differed in weight by a few grams, the difference was nearly always small and was not uniformly in favor of the group receiving the supplementary dose. In the case of the young of rat 142, the difference seems to be considerable.

TABLE 6.—*A Comparison of the Growth of Nursling Rats Fed Doses of Yeast Concentrate, Alcoholic Extract of Wheat Germ or Wheat Germ Oil, with the Growth of Litter Mates not Fed Such Supplements*

Mother Rat	Stage of Lactation, Days	Average Weight of Young Without Added Source of Vitamins B, G or E, Gm.	Average Weight of Young With Added Source of Vitamins B, G or E, Gm.	Nature of Supplement	Remarks
97	14	17	17	Marmite	
	19	20	19		
97	11	14	12	Harris' yeast concentrate	
	15	15	12	.....	2 young rats on dose dead
	21	23	21		
123	10	11	11	Harris' yeast concentrate	
	14	14	14	.....	1 young rat dead in each group
	20	18	19	.....	1 young rat dead in each group
131	10	15	15	Harris' yeast concentrate	
	14	19	19		
	17	22	22		
	21	29	29		
138	9	10	10	Harris' yeast concentrate	
	13	15	15		
	23	28	25		
142	8	11	11	Harris' yeast concentrate	
	12	15	17	.....	1 young rat on dose dead
	22	24	40		
100	14	18	17	Wheat germ oil	
	21	30	29		
107	15	33	29	Wheat germ oil	
	21	32	30		
111	14	19	19	Wheat germ oil	
	21	27	28		
120	4	6	6	Alcoholic extract of wheat germ	
	11	17	16		
	21	30	29		
124	4	9	9	Alcoholic extract of wheat germ	
	11	18	18		
	21	35	36		

It should be stated, however, that there were only two rats in each of these groups, and that the death of the smaller rat on the dosage left one unusually large rat to represent the average. It seems clear that the failure to obtain normal growth in the suckling young on high protein ration 2 was not due to a lack of either vitamin B, G or E as the single limiting factor.

Effects on the Kidneys of the Adult Females.—One of the most striking results of subjecting adult female rats simultaneously to reproduction, partial nephrectomy and a high protein intake is seen in the tremendous enlargement of the remaining kidneys. In view of the difficulties, which will be discussed later, of expressing these increases as degrees of enlargement based on some standard such as body weight, it was thought of interest to examine the data first merely on the basis of gross enlargements actually occurring, without recalculation. These data are expressed graphically in charts 1 and 2, in which all experimental animals are included, except a set of twenty rats added to the group after the graph was drawn. A wide number of variables occurred in this set of animals, the total number presented here including some older rats that had had previous litters (see table 2), as it was thought desirable to use only females with a proved reproductive capacity in the earlier part of the experiment. A more nearly homogeneous group is presented later in this discussion.

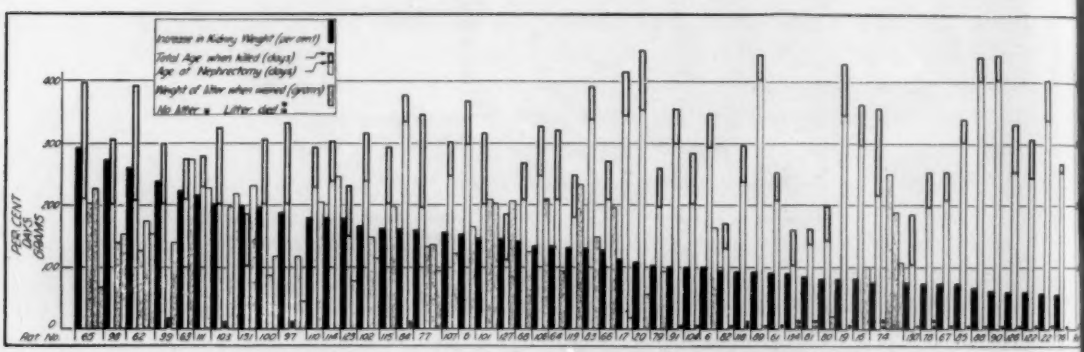

Chart 1.—Actual renal enlargement and reproduction after nephrectomy in rats on high protein rations.

On examination of charts 1 and 2, it is seen that the range of gross increase in weight of the left kidney over the right kidney removed at nephrectomy was from 295 to 57 per cent for the rats fed high protein rations, and from 137 to 13 per cent for those fed low protein rations. The records of most of the rats with successful litters are grouped near the left end of the graph, where the highest renal increases are arranged, and, for the most part, the records of the rats that either had no litters or else lost them are at the right, where the renal enlargements are of a lower order of magnitude. From even this heterogeneous set of animals it seems clear that the difference in concentration of protein between the two sets of diets is the factor of greatest significance in the renal enlargements following the removal of one kidney in this experiment, and that the influence of lactation is next in importance, pregnancy alone having less influence.

When an attempt was made to evaluate these gross enlargements on the basis of expected kidney weight, difficulties arose, as has been stated. In the first place, a discrepancy was found between the weights given by Donaldson [24] for body organs and those obtained on the rats in this experiment. A control group of ten rats obtained from the same stock as the majority of the nephrectomized animals, ranging in age from 75 to 97 days, were killed and examined and a record made of the gross body weight and the weights of the digestive tract, left kidney, right kidney and heart. The weights of the digestive tracts varied from 12 Gm. to 17 Gm., and hence this variable was relatively negligible in this instance. The deviations of the actual weights of the hearts from Donaldson's standard based on gross body weight ranged from — 0.094 Gm. to —0.172 Gm. The heart weight having the greatest deviation was only 77 per cent of the standard. That this variation was not due to the method of trimming the heart was indicated by the results of a further experiment in which possible variation due to the length of the aortic stub was determined. The heart was weighed with the stub trimmed distinctly less closely than usual and again after it had been trimmed as closely as possible. The difference was found to be approximately 1 per cent of the weight

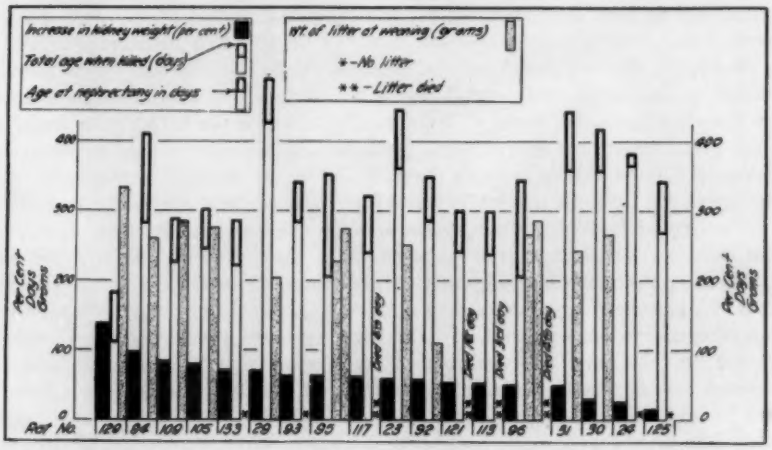

Chart 2.—Actual renal enlargement and reproduction after nephrectomy in rats on low protein rations.

of the heart. The actual weights of the two kidneys of each of the ten rats in this group were compared both with Donaldson's standard based on the body weights and with that based on the heart weights of the animals. The deviations from the former standard varied from — 0.074 Gm. to —0.359 Gm. The kidney weight having the greatest deviation was only 78 per cent of the standard. The deviations of the actual kidney weights from the standard based on the heart weights of the animals ranged from — 0.002 Gm. to — 0.362 Gm. The kidney weight having the greatest deviation was 133 per cent of the standard. Thus it can be seen that unwieldy factors of error must be used in calculating the expected kidney weight for comparison with the surviving left kidneys of the partially nephrectomized rats in this research. Furthermore, body weights were felt to be unreliable, as fluctuations of as much as 20 Gm. were frequently observed in these rats during a

24. Donaldson, H. H.: The Rat, Philadelphia, Wistar Institute, 1924.

single day without reference to continued gain or loss. The practice of MacKay and MacKay [25] in making allowance at autopsy for the observed weight of the digestive tract, a technic published after these experiments were under way, would doubtless have obviated a part of this difficulty.

In the present series of animals, other disturbing factors contributed to render the body weight obtained at autopsy unsatisfactory as a basis on which to calculate true renal enlargement. The mother rats fed high protein rations had a strikingly low amount of body fat at the twenty-first day of lactation in comparison with both the lactating rats fed low protein rations and the pregnant rats on high protein diets. The size of the normal kidney may not bear the same relationship to inert fatty tissue that it does to more rapidly metabolizing tissue. In addition, decided fluctuations in body weight at the time of autopsy had been incurred as the result of certain manipulations incident to the experiment, such as keeping some individual animals in metabolism cages for the collection of urine, or as subjecting others to the drawing of repeated blood samples during the day. As will be discussed later, some of the quantitative aspects of the experiment were deliberately sacrificed to certain qualitative aspects which were deemed essential.

Since it was evident that the body weights of the animals in these experiments were subject to such wide variations, it seemed wise to calculate the renal enlargements of the entire group of animals (table 7) on the basis of heart weights, on the assumption that the weight of the heart would be less variable. This stability of heart weight is obviously useful only to the degree that it is desirable to minimize transient gains and losses of body weight in which the kidney does not share to any great extent. It is of course possible that it might unduly minimize the significant fluctuations that would normally affect the weight of the functioning renal substance. On the other hand, MacKay [4] showed that a 5.1 per cent increase in the weight of the heart in proportion to body size was present in the mother rat from eight to twelve days after the birth of a litter, whereas if forty-five days elapsed after the normal termination of pregnancy no increase in heart size was found. If, however, the mothers were allowed to nurse their young for a period of from forty-one to forty-seven days following pregnancy, a decidedly larger increase, 10.9 per cent, in heart size was found; whether or not this augmented size was transient was not ascertained. Hypertrophy of the heart, therefore, doubtless occurred under the conditions of the present experiment, although the exact figures of MacKay do not necessarily apply in this case, in which the organs of the pregnant group were weighed either on the day following the birth of young or the day before they were expected to be born; or to the other group, in which lactation was terminated on the seventeenth or the twenty-first day.

The effect of pregnancy on renal enlargement will be brought out more clearly in table 8, in which many of the variables of table 7 have been eliminated. But it is interesting to note in passing that the general conclusions based on gross enlargements of the kidney are in agreement with those to be drawn from the data in table 7 on renal increases based on heart weight. As in the first case, so here, the greatest enlargements tend to coincide with the greatest reproductive strain in both high protein and low protein groups. The percentage enlargements for the high protein group, ranging from 219 to 29 per cent, greatly exceed those for the low protein group, which range

25. MacKay, L. L., and MacKay, E. M.: Am. J. Physiol. **83**:179, 1927.

TABLE 7.—*Renal Enlargement in Relation to Reproduction After Unilateral Nephrectomy*

Rat	Renal Enlargement Based on Weight of Heart, %	Weight of Right Kidney at Nephrectomy, Gm.	Weight of Left Kidney at Autopsy, Gm.	Weight of Heart at Autopsy, Gm.	Total Weight of Young at 21 Days, Gm.	Time After Nephrectomy on Diet, Days	Age of Rat at Nephrectomy, Days	High Protein Ration
77	219	0.967	2.504	0.741	357	172	197	2
65	193	0.745	2.947	0.925	523	187	211	2
131	160	0.686	2.047	0.723	282	83	101	2
62	151	0.607	2.187	0.514	547	180	211	2
111	148	0.811	2.571	0.950	223	58	236	2
148	143	0.542	1.412	0.567	Young died*	61	95	2
159	142	0.628	1.830	0.718	Young died†	59	96	2
63	139	0.603	1.947	0.769	272	62	211	2
100	132	0.773	2.294	0.912	206	106	201	2
115	129	0.835	2.170	0.877	195	56	237	2
68	120	0.792	1.896	0.781	126	55	211	2
79	129	0.796	1.617	0.678	90	62	197	6b
123	129	0.683	1.901	0.782	75	83	149	2
106	127	0.730	1.884	0.780	213	83	246	5
162	124	0.637	1.891	0.794	184 (17 days)	59	96	2
127	123	0.858	2.110	0.878	210	70	115	2
98	118	0.610	2.287	0.960	241	109	201	2
151	118	0.673	1.458	0.644	116 (17 days)	53	213	2
107	117	0.740	1.907	0.821	120	56	246	2
147	116	0.726	1.867	0.811	Young died†	60	95	2
156	114	0.669	1.734	0.764	Yound died*	60	95	2
114	114	0.777	2.150	0.925	244	65	237	5
99	113	0.607	2.065	0.896	139	99	201	2
83	112	0.748	1.717	0.766	148	54	337	6a
158	111	0.577	1.566	0.707	‡	60	96	2
66	108	0.878	1.976	0.879	196	60	211	2
149	108	0.616	1.752	0.792	63 (17 days)	64	95	2
119	108	0.850	1.964	0.875	235	70	178	2
102	106	0.619	1.639	0.752	308	118	201	2
104	105	0.648	1.295	0.611	‡	82	201	2
78	103	1.061	1.854	0.850	Young died§	56	197	4
150	101	0.686	1.480	0.698	134 (17 days)	57	213	2
8	101	0.764	1.923	0.886	165	60	299	1
163	90	0.543	1.337	0.647	Young died*	52	105	2
81	97	0.925	1.752	0.830	Young died§	28	134	2
101	97	0.760	1.875	0.879	311	117	201	2
157	97	0.615	1.664	0.795	‡	60	96	2
91	96	0.814	1.635	0.783	‡	58	300	3
155	95	0.645	1.486	0.725	Young died*	62	95	2
152	93	0.786	1.600	0.781	Young died*	63	213	2
165	92	0.586	1.435	0.711	Young died*	56	106	2
84	91	0.828	2.156	1.027	Young died§	40	337	2
134	89	0.620	1.198	0.612	Young died§	57	105	5
76	89	0.888	0.699	0.699	‡	64	203	4
85	88	0.902	1.565	0.782	‡	35	304	3
103	87	0.604	1.817	0.897	416	126	201	2
118	86	0.842	1.625	0.819	Young died§	62	236	5
161	86	0.555	1.506	0.766	‡	60	100	2
160	85	0.661	1.406	0.722	Young died*	61	96	2
153	82	0.668	1.575	0.812	158 (17 days)	57	95	2
126	81	0.944	1.527	0.791	‡	78	255	5
97	81	0.668	1.924	0.973	161	135	201	2
110	80	0.759	2.131	1.070	205	...	226	5
61	77	0.560	1.095	0.602	‡	40	211	2
146	76	0.721	1.580	0.838	‡	61	95	2
89	75	0.734	1.414	0.763	‡	40	403	3
164	74	0.585	1.474	0.793	Young died*	56	106	2
64	71	0.590	1.367	0.756	90	112	211	2
74	69	1.087	1.964	1.051	543	149	219	6a
6	66	0.846	1.695	0.939	164	58	291	1
82	63	0.761	1.482	0.849	‡	37	133	2
80	60	0.822	1.519	0.880	18	57	141	6a
130	60	0.568	0.907	0.602	‡	80	106	5
154	60	0.567	1.399	0.820	Young died*	62	95	2
88	55	0.884	1.487	0.888	‡	36	401	3
19	53	0.844	1.527	0.920	‡	83	345	1
16	49	1.182	2.147	1.271	100	69	298	1
20	49	0.887	1.836	1.111	56	94	356	1
67	46	0.680	1.203	0.777	‡	44	211	2
22	40	0.928	1.469	0.962	‡	69	336	1
122	29	0.716	1.166	0.841	‡	68	242	5
96	58	1.082	1.749	1.008	511	141	206	9
125	55	0.899	1.016	0.630	‡	74	255	10
94	51	0.933	1.827	1.088	260	128	283	9
105	47	0.807	1.471	0.919	275	56	246	10
93	47	0.880	1.466	0.917	‡	58	283	11
113	39	0.796	1.233	0.824	Young died§	63	257	10
92	39	0.811	1.290	0.861	110	67	283	11

TABLE 7.—*Renal Enlargement in Relation to Reproduction After Unilateral Nephrectomy—Continued*

Rat	Renal Enlargement Based on Weight of Heart, %	Weight of Right Kidney at Nephrectomy, Gm.	Weight of Left Kidney at Autopsy, Gm.	Weight of Heart at Autopsy, Gm.	Total Weight of Young at 21 Days, Gm.	Time After Nephrectomy on Diet, Days	Age of Rat at Nephrectomy, Days	Low Protein Ration
129	37	0.559	1.327	0.892	332	72	111	10
109	32	0.836	1.540	1.058	284	63	226	10
117	25	0.557	0.912	0.694	Yound died§	83	239	10
133	24	0.558	0.900	0.741	‡	65	136	10
31	23	0.915	1.377	1.022	241	86	356	8
121	20	0.658	1.022	0.796	Young died§	61	239	10
95	16	0.758	1.254	0.980	498	150	203	9
23	13	0.783	1.241	1.005	249	86	300	8
30	9	0.828	1.059	0.903	266	61	356	8
29	7	0.785	1.345	1.130	203	64	425	8

* Rat killed day before young were expected to be born.
† Rat killed day young were born.
§ Litter died from lack of milk supply or other causes.
‡ Rat did not become pregnant.

from 58 to 7 per cent, a contrast seen also in the case of gross enlargements of the kidney.

To what extent a generalization can be made on the basis of these data concerning the influence of varying concentrations of any protein in the diet is open to question. As the mineral content of the low protein diets was not corrected for the excess calcium and phosphorus in the crude casein of the high protein diets, the influence of the phosphorus in the high casein rations has not been eliminated. This is also true of the experiment of MacKay, MacKay and Addis.[26] They stated, "The protein concentrations were varied by the amount of casein in the diet and were roughly as 1 : 2 : 4. The *mineral content* and the concentration of vitamin-containing foods *were identical in each case.*" (The italics are ours.) However, an examination of the tables given in their papers shows that the mineral content of the high protein diet was 7 per cent, and that of the low protein diet (the "experimental male diet"), 5.4 per cent. Their statement must therefore be interpreted to mean that the percentage of added salt mixture was the same in the two cases, but that the mineral content of the low protein ration was not made identical with that of the high protein ration. There is no agreement at present in regard to the rôle of phosphorus in renal enlargement, but MacKay, MacKay and Addis [5] have assigned a positive influence thereto.

It was hoped that the use of cooked egg albumin as the protein in the present experiment would eliminate the high phosphorus factor to a large extent, but the performance of all the animals on egg albumin was so strikingly abnormal that no conclusions can be drawn from this part of the experiment.

The results of the present experiment afford no evidence that a high intake of yeast (1 to 3 Gm. per day) reduces the degree of renal

26. MacKay, E. M.; MacKay, L. L., and Addis, T.: Am. J. Physiol. **86**:459. 1928.

enlargement occurring on high protein diets. These results are in agreement with those of Francis, Smith and Moise.[27]

For selected groups of animals listed in table 8, calculations were made on the basis both of heart weight and of body weight.

In table 8 are summarized the records of all the animals that fall within a comparatively narrow grouping with respect to age and time on the diet. It will be seen that estimates of renal enlargement vary considerably depending on whether the calculation is made on the basis of body weight or of heart weight. By either method of calculation,

TABLE 8.—*A Comparison of the Renal Enlargements of Rats on High Protein Ration in Regard to Reproduction and Lactation*

Rats in Experiment	Average Time on Experiment, Days	Average Age of Rats in Group, Days	Average Body Weight at Nephrectomy, Gm.	Average Final Gross Body Weight, Gm.	Average Renal Enlargement Based on Body Weight, %	Probable Error	Average Renal Enlargement Based on Heart Weight, %	Probable Error	Identity of Rats in Group
Experiment 1, No Reproduction									
10	62.8	235	216	219	105.5	6.66	76.9	5.8	Nos. 61, 67, 104, 122, 126, 130, 146, 157, 158, 161
Experiment 2, Gestation Only									
13	59.3	164	217	250	111.4	3.85	98.5	4.58	Nos. 118, 147, 148, 152, 153, 154, 155, 156, 159, 160, 163, 164, 165
Experiment 3, Gestation and Lactation									
12	59.6	256	241	245	154.0	5.78	121.0	2.67	Nos. 63, 66, 68, 107, 111, 115, 119, 127, 149, 150, 151, 162

Summary

	Difference Between Renal Enlargement in Exper. 1, No. Reproduction, and That in Exper. 2, Pregnancy Only		Difference Between Renal Enlargement in Exper. 1, No Reproduction, and That in Exper. 3, Lactation		Difference Between Renal Enlargement in Exper. 2, Pregnancy Only, and That in Exper. 3, Lactation	
	Difference, Gm.	Probable Error of Difference	Difference, Gm.	Probable Error of Difference	Difference, Gm.	Probable Error of Difference
Based on body weight.....	5.9	7.7	48.5	8.7	42.6	7.0
Based on heart weight.....	21.6	7.3	44.1	7.4	22.5	5.3

however, the increase in the renal enlargement of the third group in which lactation, as well as pregnancy, occurred is considerably greater than in either of the other two groups. Statistically, the differences between them are from four to six times the probable error of the difference between the means, in spite of the fact that the probable error runs high for these small groups. When a comparison is made of the group in which no reproduction occurred with the group subjected to pregnancy only, the difference is barely significant if the estimate is based on heart weight, and not significant if based on body

27. Francis, L. D.; Smith, A. H., and Moise, T. S.: Proc. Soc. Exper. Biol. & Med. **26**:725, 1929.

weight. Under the conditions of the experiment, therefore, lactation and gestation have a much more pronounced influence on renal enlargement than has gestation alone. Although the time of autopsy of these animals in reference both to pregnancy and to lactation is different from that selected by MacKay,[4] and no such quantitative standards have herein been achieved as were possible in those experiments, the present results confirm her conclusions.

TABLE 9.—*Kidney Damage in Relation to Reproduction, Age of Female, Time After Nephrectomy and Degree of Renal Enlargement*

Subgroup, Indicating Degree of Renal Injury	Rat	Type of Injury	Time on Experiment, Days	Age at End of Experiment, Days	Total Weight of Young at 21 Days, Gm.	Weight of Right Kidney at Nephrectomy, Gm.	Weight of Surviving (Left) Kidney, Gm.	Renal Enlargement on Basis of Body Weight, %
Group 1. Rats Having Previous Pregnancies at Connecticut Agricultural Experiment Station; High Protein Ration; Partial Nephrectomy								
A	77	Severe	172	309	357	0.967	2.504	...
B	74	Slight	149	308	543	1.087	1.964	...
Group 2. Rats Having Previous Pregnancies at Connecticut Agricultural Experiment Station; Low Protein Ration; Partial Nephrectomy								
C	94	No injury	128	411	260	0.933	1.827	..
	95	No injury	150	353	498	0.758	1.254	...
	96	No injury	141	344	511	1.082	1.749	...
	Average group 2.....		140	369	423	0.924	1.610	...
Group 3. Rats Having No Previous Pregnancies, Obtained from Stock Colony on Modified Sherman Ration; High Protein Ration; Partial Nephrectomy								
A	62	Severe	180	391	547	0.607	2.187	228
	65	Severe	187	398	523	0.745	2.947	229
	Average group 3A.....		184	395	535	0.676	2.567	229
B	100	Slight	106	307	206	0.773	2.294	160
	103	Slight	126	327	416	0.604	1.817	162
	Average group 3B.....		116	317	311	0.689	2.056	161
C	64	No injury	112	323	90	0.590	1.367	168
	97	No injury	125	336	161	0.668	1.924	157
	98	No injury	109	310	241	0.610	2.287	240
	99	No injury	99	300	139	0.607	2.065	194
	101	No injury	117	318	311	0.760	1.875	138
	102	No injury	118	319	308	0.619	1.639	140
	Average group 3C.....		115	318	208	0.642	1.860	173

In the present investigation, the remaining kidney of each of the experimental animals fed a high protein ration for a period of ninety days or longer after nephrectomy and of thirty-nine individuals for shorter intervals was examined histologically. Since none of these animals fed the high protein rations for less than 106 days after nephrectomy showed injury of the kidney, sections were not made of the kidneys of the remaining animals of the group. The data on the kidneys of all of the rats that were on the experiment for intervals longer than ninety-five days are recorded in table 9 for comparison.

In only three individuals of the whole number examined were severe lesions of the kidneys found; in three others, moderate injury. The severe lesions corresponded closely to those found in rats 150 days after nephrectomy by Moise and Smith [28] and Smith and Moise,[17] and the moderate ones to those described as occurring after intervals of from 90 to 120 days. The lesions presented in photomicrographs by these authors represent accurately the changes observed in this investigation.

Two of the animals showing renal injury, one with severe and one with moderate lesions, are listed separately as group 1 in the tables, because they belong to the set of older rats with a record of pregnancies prior to the experiment. It is noteworthy that three other rats from this same set of animals which had previously borne young and were fairly comparable in regard to the time during which they were the subject of experiment, age and total weight of young, but which were fed a low protein diet (group 2), did not show any renal injury. Therefore, the renal changes observed in the animals in group 1 presumably did not antedate the present investigation. The rats in group 3 were a uniform group of virgin females fed a modified Sherman ration, and later partially nephrectomized and fed the same experimental ration as group 1. The variations in time on the diet are accounted for by the fact that repeated pregnancies were attempted. Rat 64 had one pregnancy; rats 97, 98, 99, 100, 101 and 102 had two pregnancies each, and rats 62, 65 and 103 had three pregnancies each. When the records in this table are examined, it is evident that, in general, it is the rats subjected to the greatest reproductive strain for the longest time on a high protein ration that show evidence of renal damage. In group 3 the two rats having the greatest injury of the kidney also have, with a single exception, the greatest renal enlargements in this group; rat 98 with no renal damage is the only one the renal enlargement of which exceeds these. It should be noted that renal enlargement in this set of lactating animals is strikingly greater than that found by Smith and Moise [2] in male rats on a diet containing 85 per cent of crude casein, yet kidney damage certainly appears no earlier in this experiment, and if the record of so few animals may be taken as evidence, its onset is even slower in these females than in the experimental animals of Moise and Smith. It seems probable, therefore, that the influences determining the degree of renal enlargement on a high casein ration are not altogether identical with those producing kidney damage. This point will receive fuller discussion in a following paper.

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28. Moise, T. S., and Smith, A. H.: Effect of High Protein Diet on Kidneys: Experimental Study, Arch. Path. **4**:530, 1927.

Effects on the Kidneys of the Young.—In chart 3 are arranged the ratios of the average body weights [29] to kidney weights at the twenty-first day post partum of litters from mothers with different nutritional and operative histories. It is plain that there is a tendency at 21 days of age for the young of the nephrectomized mothers on a high casein ration to have larger kidneys in proportion to their body weights than

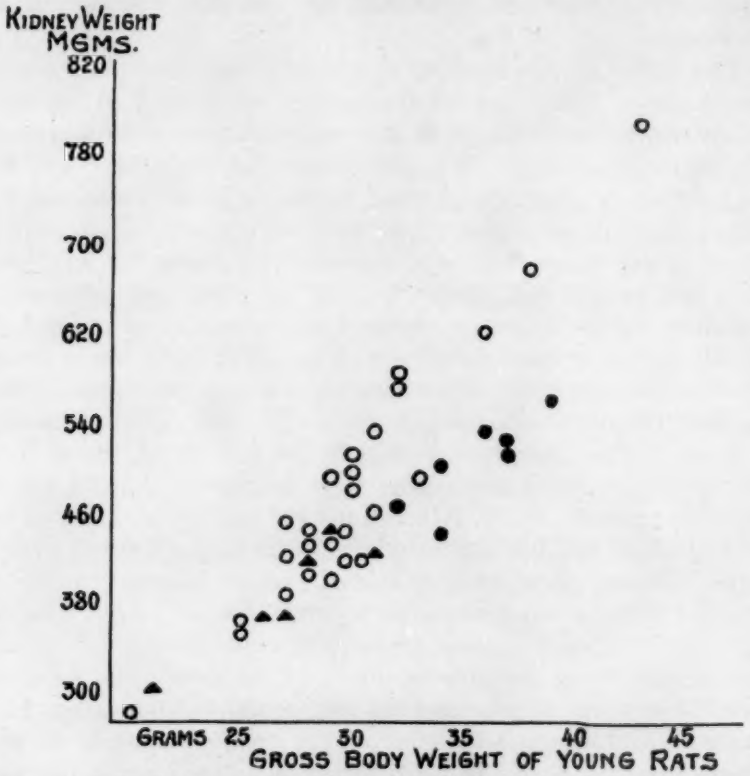

Chart 3.—Ratios of the average body weights to kidney weights at the twenty-first day post partum, of litters from mothers with different nutritional and operative histories. The circles represent the offspring of mothers (one kidney) fed a high protein diet; the triangles, offspring of mothers (two kidneys) fed a high protein diet, and the solid circles, offspring of mothers (one kidney) fed a low protein diet.

the young born from mothers on a low casein ration. The former, however, do not differ noticeably in regard to proportional kidney weight from the young born from intact mothers on a high casein

29. In most cases, the litter was divided, and the data were obtained for the males and the females separately. Any individual strikingly different in size from the rest of the litter was discarded.

ration. The exact interpretation of this divergence is not clear. At this age, the young have been nibbling a variable amount of the mother's ration for three or four days in addition to the mother's milk supplied to them. Osborne, Mendel and associates [6] observed an increase over the standard given by Donaldson in the weight of the kidneys of rats that had been fed a high protein diet for so short a period as three days,

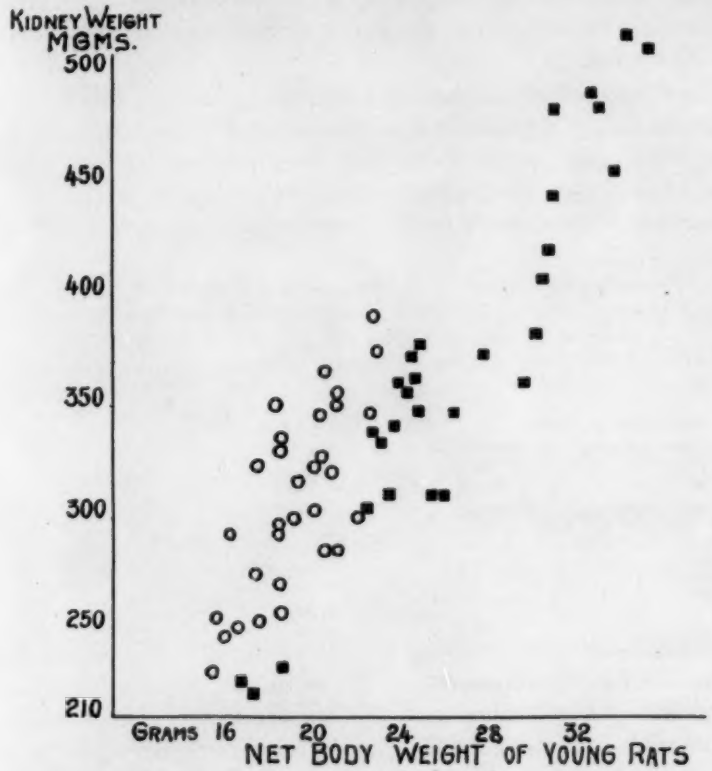

Chart 4.—Ratios of the average body weights to kidney weights at the seventeenth day post partum, of litters from nephrectomized mothers on a high protein diet, compared with similar data on litters from intact mothers on a stock ration comparatively low in protein. The circles represent the offspring of mothers (one kidney) on high protein diet; the squares, offspring of mothers (two kidneys) on low protein diet.

in contrast with the performance of other rats fed rations low in protein. Smith and Moise [2] recorded a 49 per cent renal enlargement accompanied by a 44 per cent increase in total solids in a three day interval after nephrectomy on a high protein diet. Although the suckling young in the present investigation were deriving only a part of their food supply from the mother's ration during the brief interval,

it was realized that this might have been sufficient to account for the enlargement observed, in view of the results noted. A further experiment was therefore carried out. The young of rats 149, 150, 151, 153 and 162 on high protein ration 2 were killed at the age of 17 days before any were observed to have visited the mother's food cup. Litters from intact females on the modified Sherman ration were also killed at the same age. The net body weight was obtained by the method of MacKay and MacKay,[25] and the weight of the two kidneys was obtained for each animal.

The results shown in chart 4 and table 10 indicate that at 17 days of age the young of nephrectomized mothers on a high casein diet have larger kidneys in proportion to their body weights than the young of intact mothers on a stock ration comparatively low in protein. Certain implications of these results will be considered in succeeding papers.

TABLE 10.—*A Comparison of the Relative Kidney Weights of 17 Day Old Rats from Intact Mothers on Modified Sherman Ration and Partially Nephrectomized Mothers on a High Protein Ration, Respectively*

Character of Group	Mean Ratio of Body Weight to Kidney Weight	Probable Error	Significance Ratio $\frac{D}{PED}$
Twenty-nine offspring of mothers (two kidneys) on modified Sherman ration	73.8	0.755	8.5
Thirty-one offspring of mothers (one kidney) on high protein ration 2	64.8	0.735	

CONCLUSIONS

Lactation and gestation have a greater influence than gestation alone on the degree of enlargement of the remaining kidneys in rats fed a high casein diet following unilateral nephrectomy. These results are in agreement with those of MacKay in her quantitative study of intact female rats on a lower protein ration.

Renal lesions were observed in a few of the rats that were subjected to the greatest reproductive strain and that were fed a diet rich in protein for periods varying from one hundred and six to one hundred and eighty-seven days.

The kidneys of the young born from mothers fed high casein rations weigh more in proportion to body weight at weaning than do those of the young of females given rations comparatively low in protein.

The rations rich in casein (86 and 76 per cent) are less satisfactory for successful lactation than others containing less of this protein (20 per cent) but the same allowance of vitamin-rich foods.

A COMPARISON OF THE INTRANUCLEAR INCLUSIONS PRODUCED BY THE HERPETIC VIRUS AND BY VIRUS III IN RABBITS*

E. V. COWDRY, PH.D.

ST. LOUIS

Thus far the subject of the production of intranuclear inclusions in virus diseases has been treated rather lightly. The interest of many investigators has ceased with the demonstration that the particular inclusions in question are definitely associated with the action of a special virus. Some have delved a little more deeply, with the object of discovering, if possible, whether the inclusions are combinations between virus and nuclear material, or simply altered nuclear substance —without being able to reach a decision which is generally acceptable. Few have felt impelled to investigate closely the formation of single kinds of inclusions, that is, to concentrate on limited aspects of the problem.

Instead there has been a marked tendency to generalize concerning a large and expanding group of diseases some of which have but little in common. Why certain of these diseases cause inclusions in the nuclei, others in the cytoplasm, others in both and why still others fail to produce inclusions in either situation one does not know. One is equally in the dark as to the cytologic changes involved in the stimulation to cell division effected by some viruses, the cellular hypertrophy caused by others, the rapid death and quick lysis caused by others and conversely the slow death and strange persistence of dead cells resulting from the action of still another virus. How the viruses do these things one does not know. There has been no correlation between their action on living cells and their physical properties.

Even the fundamental cytologic question of the similarity or the dissimilarity between the intranuclear inclusions that are produced by a half dozen or more viruses has been only partly answered despite the fact that these inclusions can almost be regarded as the footprints of the viruses and thus afford a desirable point of departure for cytologic studies.

After describing the intranuclear inclusions in "visceral disease," von Glahn and Pappenheimer [1] concluded: "There can be no doubt

* Submitted for publication, Feb. 3, 1930.

* From the Anatomical Laboratory, Washington University School of Medicine.

1. Von Glahn, W. C., and Pappenheimer, A. M.: Intranuclear Inclusions in Visceral Disease, Am. J. Path. **1**:445, 1925.

that the inclusions are identical in their morphology and staining reactions with the bodies seen by previous observers in the viscera of infants, and by Lipschütz and others in the tissues of spontaneous and experimental herpes, and in various neural and visceral lesions produced by the herpetic and related viruses." They further stated that the virus isolated by Rivers and Tillett (later called virus III) produced ". . . intranuclear inclusion bodies apparently identical with those described in herpes. . ."

Obviously, the force of the word identical is measured by at least three considerations: first, the number of the properties considered; second, the accuracy attained in their determination, and third, the degree of parallelism in the conditions of observation of the substances compared. Von Glahn and Pappenheimer did not mention the fixative used, but it is likely that they employed several kinds. This makes it difficult to evaluate the results which they secured by using the stains of Gram, Mallory, Bensley, the Levaditi technic and scharlach R. For instance, they described the inclusions as "vividly red" by the Bensley method, whereas by the same technic Goodpasture characterized the herpetic bodies as remaining "unstained or faintly green." This does not look like identity unless the conditions of examination were different. From perusing the paper, one gains the impression that the only inclusions actually studied by von Glahn and Pappenheimer were those in visceral disease, reliance being placed for the properties of the others on descriptions in the literature which are themselves meager in the extreme.

This is just an example. Other unsupported assertions of similarity between the inclusions caused by different viruses, which if true would argue against their specificity, are current in the literature. Goodpasture [2] stated that "similar" intranuclear inclusions occur in "three human diseases, herpes simplex, herpes zoster and varicella." Cole and Kuttner [3] wrote: "Nuclear changes which cannot at present be differentiated from those occurring in the lesions of spontaneous and experimental herpes simplex also occur in the skin lesions of herpes zoster, in the skin lesions of varicella, and in the lesions experimentally produced in rabbits by the Virus III of Rivers and Tillett. . ." Later, describing the inclusions in the meningeal exudate produced by the submaxillary virus in guinea-pigs, they said: "These cells resemble in all particulars the cells containing nuclear inclusion bodies which occur in herpes simplex and related conditions," but they did not specify what the particulars are. More recently,

2. Goodpasture, E. W.: Intranuclear Inclusions in Experimental Herpetic Lesions of Rabbits, Am. J. Path. **1**:1, 1925.

3. Cole, R., and Kuttner, A. G.: A Filterable Virus Present in the Submaxillary Glands of Guinea Pigs, J. Exper. Med. **44**:855, 1926.

Torres [4] expressed the belief that the intranuclear inclusions in experimental yellow fever in monkeys are of the same nature as others discovered in herpes simplex, symptomatic herpes, varicella and virus III disease of the rabbit and described sometimes under the heading of oxychromatic degeneration.

It remains to be shown just how close these "identities" and "similarities" are, because it is possible that with the use of more discriminating methods, unsuspected differences will be brought to light, although from the cytologic point of view a certain monotony or fixity in nuclear response to diverse agencies is to be expected because the nuclei are sheltered from environmental changes by a layer of adaptable and shock-absorbing cytoplasm. Moreover, the available reactive material in the nucleus is strictly limited in quality as compared with that found in the cytoplasm, which means that the intranuclear inclusions, bound as they must be to some extent by this restriction, would tend to be alike chemically, and this is in fact the case.

In a recent study, I observed [5] that the intranuclear inclusions in chickenpox, herpes, submaxillary disease of guinea-pigs and virus III disease of rabbits are characterized by their resistance to solvents in various kinds of fixatives and by the fact that they contain little or no thymonucleic acid and iron in organic combination. But while comparing the intranuclear inclusions caused by the virus of yellow fever with those in other virus diseases, in cooperation with Dr. S. F. Kitchen,[6] I observed some unexpected morphologic differences.

It is in the belief that before one makes any generalizations one needs more accurate information concerning individual types of inclusions that this contribution is offered. The inclusions characteristic of herpetic and virus III infections were selected for study because their properties can be conveniently compared under exactly parallel conditions in the testicles of rabbits.

EXPERIMENTAL METHOD

Three experiments were carried out. The technic of the first is given in detail:

Two rabbits were selected of about the same weight. The testicles of one were inoculated with a saline emulsion of glycerinated rabbit's brain infected with H. F. herpes virus, and those of the other with a saline emulsion of fresh rabbit

4. Torres, C. M.: Inclusions nucléaires acidophiles (dégénérescence oxychromatique) dans la foie de Macacus rhesus inoculé avec le virus brésilien de la fièvre jaune, Compt. rend. Soc. de biol. **99**:1344, 1928.

5. Cowdry, E. V.: The Microchemistry of Nuclear Inclusions in Virus Diseases, Science **68**:40, 1928.

6. Cowdry, E. V., and Kitchen, S. F.: Intranuclear Inclusions in Yellow Fever, Am. J. Hyg. **11**:227, 1930.

testicle infected with virus III. After forty-eight hours, the animals were killed and the testicles removed. Both pairs of testicles were definitely affected, but those from the animal inoculated with virus III showed the most pronounced lesions macroscopically.

The testicles from the herpetic rabbits and those inoculated with virus III were cut in transverse sections, about 2 mm. thick. The sections from the herpetic rabbit were immediately placed in bottles containing special fixatives, but those of the testicles of the rabbit inoculated with virus III were first hemisected so that pieces of tissue were secured of half the size and of conspicuous shape (for identification), but of the same thickness as those employed from the herpetic rabbit so that the fixative would penetrate both at the same rate. One of these was placed in the same bottle with each piece of herpetic tissue at as nearly as possible the same moment. The tissues fixed in this manner side by side in the same bottle were washed, dehydrated, cleared and finally embedded together in the same block of paraffin. Sections were cut at the same thickness (4 microns) and were mounted on the same slide so that in all the subsequent tests the comparison between the herpetic and the virus III inclusions was direct. The fixatives employed in this first experiment were as follows: (1) carnoy (absolute alcohol 18 cc., chloroform 9 cc., acetic acid 3 cc.); (2) carnoy 70 cc., plus chloroform 10 cc.; (3) carnoy 10 cc., plus chloroform 20 cc.; (4) carnoy 5 cc., plus chloroform 20 cc.; (5) pure chloroform; (6) 95 per cent alcohol (ethyl); (7) saturated aqueous corrosive sublimate 10 cc., plus absolute alcohol 10 cc.; (8) Zenker's solution without acetic acid 10 cc., plus 2.5 cc. commercial formaldehyde; (9) Zenker's solution 15 cc., plus 5 cc. acetic acid; (10) Zenker's solution 10 cc., plus 10 cc. acetic acid; (11) Zenker's solution 5 cc., plus 15 cc. acetic acid, and (12) Zenker's solution 1 cc., plus 19 cc. acetic acid. The object of using the first five fixatives was to test the effect on both types of inclusion, of a progressive increase in the concentration of chloroform. The purpose of employing the last four fixatives was to determine the effect on the inclusions of an increase in the concentration of acetic acid.

In experiment 2, the same method was followed, except that the herpetic emulsion was made from fresh infected rabbit's brain instead of from glycerinated material. This gave more pronounced herpetic inclusions. The same kinds of fixatives were employed.

Experiment 3 was made as a further control, because in experiment 2 some bacteria were noted in the testicles infected with virus III. The tissues were fixed in a different series of fixatives, namely: (1) Acetic acid 2 drops, 2 per cent osmic acid 4 cc., and 2.5 per cent potassium dichromate 16 cc.; (2) Regaud's solution (3 per cent potassium dichromate 20 cc., commercial formaldehyde 5 cc.); (3) a dilute solution of formaldehyde, U.S.P. (1:10); (4) Zenker's solution without acetic acid; (5) Zenker's solution plus 5 per cent acetic acid; (6) Zenker's solution plus a dilute solution of formaldehyde, U.S.P. (1:10); (7) 95 per cent alcohol; (8) 95 per cent alcohol saturated with corrosive sublimate; (9) 1 per cent silver nitrate; (10) 95 per cent alcohol 25 cc., plus 1 drop of ammonia, three hours, then washed in water and placed in 1 per cent silver nitrate.

These experiments yielded an abundance of tissue for microchemical analysis. The overlapping and duplication were essential because the lesions were never spread uniformly throughout the entire extent of the testicles, so that sometimes areas severely injured by one virus would be compared with tissues lightly affected by the other. When

this occurred, the material from the other experiments was usually found to fill in the gaps. The herpetic virus caused more infiltration and injury of the interstitial tissue, while virus III proved in all cases to be more invasive; that is to say, a larger variety of cells exhibited typical intranuclear inclusions. By it they were produced in the following situations: (1) endothelial cells, (2) macrophages, (3) interstitial cells, (4) spermatogonia, (5) spermatocytes I and II (occasionally) and (6) epithelial cells of the tubuli recti, canals of the rete, ductuli efferentes and ductus epididymis. The herpetic inclusions were confined to the endothelial cells and macrophages, which necessitated a limitation of the comparison to these two kinds of cells. Both inclusions in all three experiments were first examined after coloration in the same manner with samples of Giemsa's stain taken from the same bottle. In this way, the proportion of red and blue dyes was held constant and care was taken to differentiate the stain as far as possible to the same degree.

MORPHOLOGY

On comparing the sections colored by Giemsa's stain, a marked difference in the morphology of the inclusions caused by herpes and by virus III was at once observed. This is illustrated in figures 1 to 4. The half figures in the column to the left and marked *A* show herpetic inclusions, and those to the right and marked *B*, virus III inclusions. In the case of each figure, *A* and *B* are directly comparable, being photomicrographs of tissues prepared in the same way and mounted side by side on the same slide.

Even a cursory examination shows that in the herpetic lesions the inclusion material is finely granular and occupies almost all of the intranuclear space (*A*, figs. 1 to 4); while, in the case of virus III, it is drawn together into a dense mass in the center of the nucleus, leaving a clear area between it and the surrounding nuclear membrane (*B*, figs. 1 to 4). These dense intranuclear inclusions in testicles infected with virus III frequently assume the general shape of the nuclei in which they are found.

A detailed study of the figures reveals still more. In figure 1, the nucleus to the extreme left containing a herpetic inclusion is much more hyperchromatic than the nucleus to the right (in the upper part of *B*) containing a virus III inclusion; in other words, the chromatin is more thickly and irregularly marginated on the nuclear membrane.

In figure 2, substantially the same differences are noted, notwithstanding the fact that the amount of chloroform in the fixative was greatly increased. The herpetic inclusion in *A* is finely divided, whereas the virus III inclusion in the upper left corner of *B* is compact. The halo about the latter is, however, not so clear from visible formed material as in *B*, figure 1. The contour of the virus III inclu-

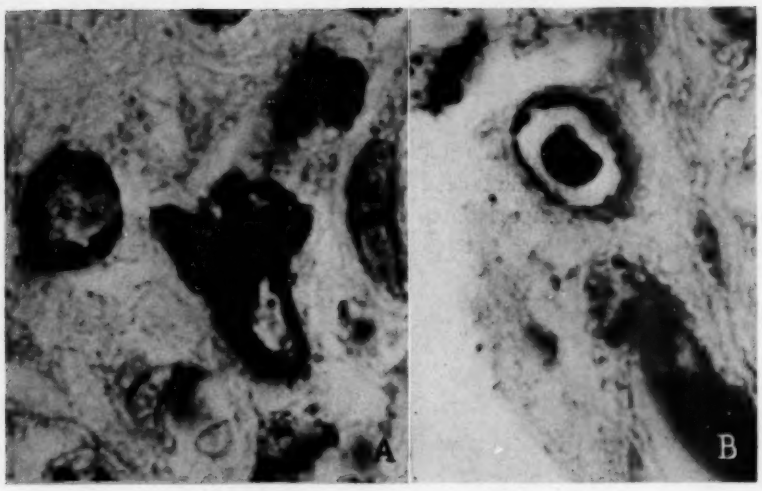

Fig. 1.—Intranuclear inclusions after fixation in Carnoy's fluid and coloration by Giemsa's stain: *A*, herpes, and *B*, virus III; × 2,000.

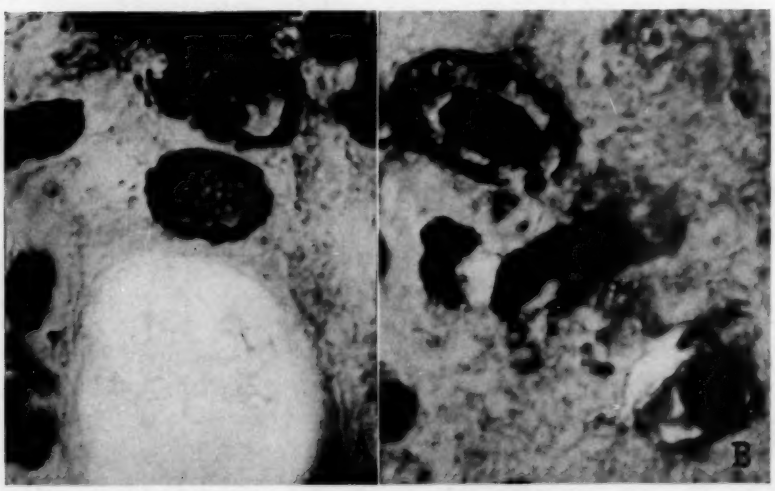

Fig. 2.—Intranuclear inclusions after fixation in equal parts of Carnoy's fluid and chloroform and coloration by Giemsa's stain: *A*, herpes, and *B*, virus III; × 2,000.

sion follows that of the limiting nuclear membrane. Another nucleus provided with a virus III inclusion is to be seen in the lower right hand corner of figure 2 *B*. Hyperchromatism is marked.

Figure 3 illustrates the same differences, except that the coloration is much lighter because Zenker's fluid was used as a fixative instead of Carnoy's fluid with high content of chloroform. The outline of the nucleus containing the herpetic inclusion a little to the right of the center of *A* is less sharp owing to the direction of the section than the outlines of the two nuclei with virus III inclusions.

Finally in figure 4, corresponding differences between the two types of inclusions are again revealed. The nuclei laden with herpetic and virus III inclusions are in the lower right hand corners of *A* and *B*, respectively.

Such differences in morphology were the rule in all three experiments, after the use of the wide range of fixatives enumerated, with the exception of the last named (alcohol followed by silver), which did not reveal inclusions of either kind. They were not conditioned by the stain employed, because this was the same in all instances and because stains do not alter structural details once these have been fixed, but merely color them. The differences were equally apparent after the use of hematoxylin and eosin, iron hematoxylin, fuchsin-methyl green and other dye combinations.

Both types of inclusion show some variability dependent on their size or maturity at this time of forty-eight hours after inoculation of the viruses. A few of the nuclei (perhaps 0.5 per cent) are provided with finely divided inclusions which would be difficult to distinguish from the herpetic ones, but none of the herpetic inclusions are so compact as the inclusions caused by virus III.

STAINING REACTIONS

The staining reactions were measured by comparing the stained inclusions with colors as standardized by Ridgway.[7] The source of illumination was held constant and consisted of a large Spencer lamp containing a General Electric projection Mazda 400 watt, 115 volt bulb.

The experiments showed that both types of inclusions may easily be colored in any way that is desired by selecting the necessary fixatives and stains and by varying the degree of differentiation. Thus, they tend to be redder after Zenker's fluid, bluer after Carnoy's fluid and greener after fixation in the acetic-osmic-bichromate mixture when Giemsa's stain has been applied in exactly the same way. These

7. Ridgway, R.: Color Standards and Color Nomenclature, Washington, D. C., 1912.

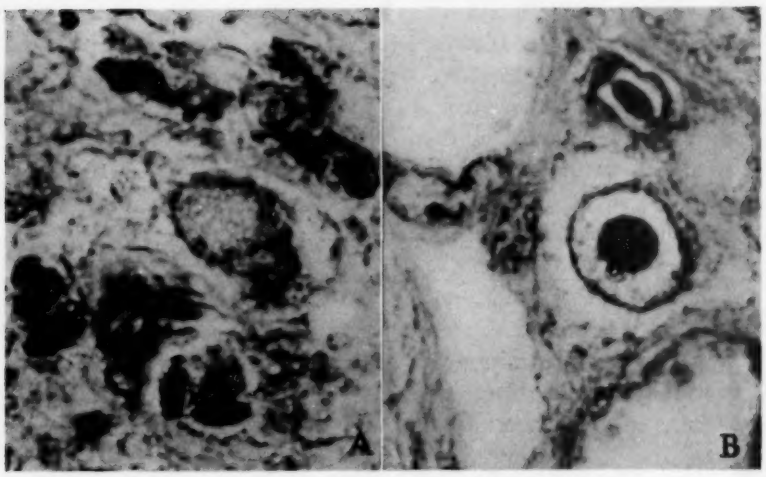

Fig. 3.—Intranuclear inclusions after fixation in Zenker's fluid 20 cc., plus acetic acid 5 cc., and coloration by Giemsa's stain: *A*, herpes, and *B*, virus III; × 2,000.

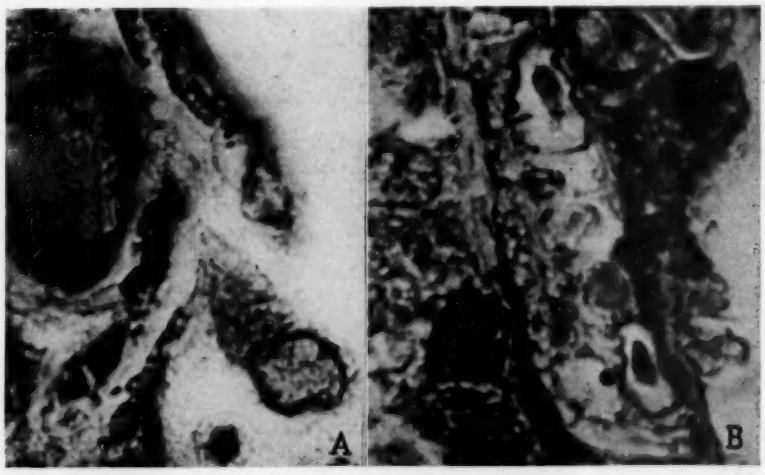

Fig. 4.—Intranuclear inclusions after fixation in Zenker's fluid 10 cc., plus acetic acid 10 cc., and coloration by Giemsa's stain: *A*, herpes, and *B*, virus III; × 2,000.

tendencies resulted from mordanting during the process of fixation and were to be expected.

Though both the herpetic and the virus III inclusions are chiefly acidophilic in their affinities; that is to say, they are themselves basic and take up acid dyes like eosin, there is a variation in this property.

For example, in experiment 2 after fixation in Carnoy's fluid and staining by Giemsa's method, the herpetic inclusions exhibited a transition in color from LaFrance pink to Phlox pink, whereas the virus III inclusions were of a color like Bradley's violet, which is much darker and bluer. The same difference held when the concentration of chloroform in Carnoy's fluid was increased. It was also noted after preservation in Regaud's fluid, a dilute solution of formaldehyde, U. S. P. (1:10), sublimate alcohol and Zenker's fluid containing different concentrations of acetic acid. Evidently, therefore, there is a tinctorial distinction between the inclusions characteristic of herpetic and of virus III infections, the latter being rather more basophilic.

Both viruses yield nuclei in various stages of the reaction, often side by side. When only a few fine acidophilic particles are present, the color of these particles is always less intense than when they are present in larger numbers or are fused to form a large compact mass. This is true for both kinds of inclusions. The reason why the virus III inclusions are in general bluer after Giemsa's stain than the herpetic inclusions may be merely because they are denser and more compact. With greater density, the blue component of the dye might be extracted more slowly on differentiation.

Thus far, reference has been made only to the tinctorial properties of the predominating material making up the inclusions. When the inclusions are well formed, two other components may occasionally be recognized, though in the majority of cases they are absent.

The first of these is a series of small chromophobic vacuoles. Each inclusion may contain only one or two such vacuoles, or else its whole substance may exhibit a foamy appearance, the only stainable material being in the continuous matrix. These watery vacuoles are not so often seen in the finely divided particulate herpetic inclusions as in the denser virus III inclusions.

The second consists of very tiny, roughly spherical masses of material which color intensely with basic dyes. These basophilic bodies are of inconstant occurrence in both types of inclusion.

MICROCHEMISTRY

The aforementioned tinctorial reactions of the inclusions are not of great significance from the point of view of microchemistry. The fact that when the inclusion material is present rather diffusely in finely

divided form it stains less intensely and in a more acidophilic way than when it is aggregated in a compact mass does not of necessity indicate a difference in chemical constitution. The difference in staining reaction may be due to a mass effect, the blue component of the stain being extracted more slowly from large masses of inclusion material than from smaller ones. The observation that the inclusions in virus III infections tend to be more basophilic than herpetic inclusions when tested under parallel conditions may be explained on the same basis, for they are in general much denser when both are examined forty-eight hours after inoculation.

Both types of inclusion are resistant to the solvent action of fixatives, indicating a protein constitution. They are not destroyed by 95 per cent alcohol or a dilute solution of formaldehyde, U. S. P. (1 : 10), when these chemicals are used alone. The concentration of chloroform in Carnoy's fluid can be increased to slightly over 80 per cent without injuring them. Pure chloroform distorts the nuclei greatly, but traces of virus III inclusions may still remain. The persistence of the herpetic inclusions is doubtful. The percentage of acetic acid in Zenker's fluid can be increased to 95 without dissolving either kind of inclusion. This would at first appear to indicate great resistance to acetic acid, but the acetic acid is applied in association with potassium bichromate and corrosive sublimate, which may inhibit its solvent action. The reason for this reservation is that Cowdry and Kitchen [6] observed that the intranuclear inclusions characteristic of experimental yellow fever in monkeys withstand a high percentage of acetic acid in both Zenker's and Carnoy's fluid, but are readily dissolved when 0.1 per cent acetic acid is applied to them in the fresh state.

Neither the herpetic nor the virus III inclusions give definitely positive Feulgen reactions for thymonucleic acid. It is noteworthy, however, that only rarely are inclusions observed which remain entirely uncolored after application of the reagents to the same degree that the red blood cells and all cell membranes remain uncolored. This complete absence of color reaction was established after long study in some of the least developed and most finely granular herpetic inclusions. The larger herpetic inclusions are often extremely lightly stained, but to measure the color is a difficult matter. In quality, it resembles closely the rose pink of Ridgway's scale but its intensity is less. It never approaches in strength the dark aster purple of the chromatin marginated on the nuclear membrane which is giving a typically positive Feulgen reaction. Whether the color of the herpetic inclusions is sufficiently marked to justfy the listing of the majority of herpetic inclusions as feebly positive is doubtful.

The virus III inclusions react a little more strongly. It is rare to find any which do not exhibit just a tinge of rose pink. In the case of the most compact ones, the rose pink is replaced by a light mallow purple. But this mallow purple is still very much lighter than the color taken by the nuclear chromatin. It is not unusual to find in the testicles inoculated with virus III that some of the halos separating the inclusions from the surrounding nuclear membranes are themselves evenly colored a pale rose despite the fact that they are devoid of visible contents.

The Feulgen reaction only in rare instances gives evidence of the existence of two kinds of material within individual inclusions both in herpetic and in virus III infections. Almost always the color or lack of color is uniform throughout the inclusions. Tiny vacuoles are, however, sometimes present, which do not stain and which have been previously referred to. In addition, one or as many as five or six intensely colored particles may be distinguished within the inclusion. These are the inconstant basophilic bodies already described. They are colored just like the marginated chromatin, and there is no reason to believe that they are anything other than very occasional traces of incompletely marginated material.

These tinctorial differences given by the Feulgen reaction would be devoid of significance were it not for the remarkable constancy and regularity in the results secured. Indeed, this reaction is the easiest of all microchemical tests to employ, provided that care is taken not to use fixatives containing potassium bichromate or osmic acid. The results described were obtained without any noticeable deviation after fixation in 95 per cent alcohol, Carnoy's fluid and alcoholic sublimate.

COMMENT

From the observations described it is clear that forty-eight hours after inoculation of the testicles of rabbits with active virus, the intranuclear inclusions produced by herpes and by virus III in these testicles can easily be distinguished from each other on morphologic criteria. The virus III inclusions are much more compact than the herpetic ones. Too much confidence should not be placed in the tinctorial differences brought to light because of the large experimental error existing in cytologic technic. But the Feulgen reaction showed that both types of inclusion contain little or no thymonucleic acid, and their solubilities indicate a protein composition. Whether the intranuclear inclusions caused by these two viruses can be equally clearly distinguished in the earliest and in the latest stages of the injury remains to be determined, for in this investigation the tests have been applied, under comparable conditions, only to a single stage in their evolution.

The principal theory concerning the nature of the inclusions originated with Lipschutz and has been supported by Goodpasture and his associates. Goodpasture and Teague [8] wrote:

> The constancy with which the intranuclear bodies occur and the characteristic morphological and tinctorial properties which they present in experimental lesions of herpes febrilis in rabbits have convinced us that they represent, as Lipschutz claims, the presence and growth, within the nucleus, of the specific virus of the disease. It seems probable also that the virus itself may be obscured by a mantle of nuclear material which gives to the inclusions their usually homogeneous appearance and acidophilic staining quality. . . . We have observed, especially in the cells of the ovary and brain, a more basophilic staining reaction and a more granular appearance of the inclusions within nuclei filled with the included mass, and this may possibly be due to an overgrowth of virus and a suppression in the formation of surrounding material.

In another place,[9] these authors referred to their contention "that the intranuclear bodies are essentially masses of virus."

A little later Goodpasture [10] expressed the same view with qualifications:

> It seems evident, however, that the material which constitutes the "inclusion" may partly at least be composed of coagulated nucleoplasm which may impart the acidophilic staining property of the inclusions. It is to be noted, however, that when the minute granulations are discrete enough to be recognized as such they stain faintly basophilically, whereas the precipitate from the nucleoplasm of normal cells is more acidophilic. They are to be regarded at present as elementary bodies taking part in the structure of the herpetic inclusions.

Finally, in his most recent paper Goodpasture [11] said, in respect to herpes and rabies, that morphologic data indicative of micro-organisms as active agents are not convincing; and, further,[12] he said:

> So long as we conceive of virus diseases as infections due to living agents there is the obvious implication of a possibility of identifying these agents morphologically and of cultivating them on a non-living medium, thus submitting them to a more intensive study. On the other hand, if they are interpreted to be reproduced only through the action of living cells of the host, it would seem useless to continue efforts in the direction of cultivation on a lifeless medium.

Here, I agree entirely with Goodpasture, except that, with the meager knowledge, I do not think it advisable to espouse any interpretation.

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8. Goodpasture, E. W., and Teague, O.: Experimental Production of Herpetic Lesions in Organs and Tissues of the Rabbit, J. M. Research **44**: 121, 1923.

9. Goodpasture, E. W., and Teague, O.: Transmission of the Virus of Herpes Fibrilis Along Nerves in Experimentally Infected Rabbits, J. M. Research **44**:139, 1923.

10. Goodpasture (footnote 2).

11. Goodpasture, E. W.: Cellular Inclusions and the Etiology of Virus Diseases, Arch. Path. **7**:114, 1929.

12. Goodpasture, E. W.: Herpetic Infection, with Special Reference to Involvement of the Nervous System, Medicine **8**:223, 1929.

The evidence as it stands is insufficient to justfy the contention that the inclusions are masses of virus or even that they are partly made up of virus. The minute granulations within the inclusions, which stain faintly basophilically and on which Goodpasture is inclined to rely, are, as he admits, to be seen only rarely—indeed, their presence is much more the exception than the rule—whereas active virus is present somewhere in the affected tissues in great abundance. No proof has been offered that in the case of these ill defined granules one is dealing with anything other than finely divided nucleoprotein which is a little more acid in its reactions (i. e., more basophilic) than the rest of the inclusion material. In nuclei in the process of degeneration it is natural to find variations in the reaction of nucleoprotein, which is so characteristically an amphoteric substance. A slight shift in the iso-electric point would be expressed by variation in the response to acid and basic dyes. When it comes down to details, the color taken by materials within the nucleus when stains are applied depends so much on fixation, mordanting and degree of differentiation that it is unsafe to base conclusions on any except pronounced differences in tinctorial properties. I do not wish to deny that virus III and the virus of herpes enter the affected nuclei. They may or they may not do so, but the evidence which has been offered that the viruses are actually microscopically visible within the injured nuclei is not, in my opinion, convincing.

One can only speculate as to how the inclusions are produced. There are many possibilities which are difficult to test experimentally. The viruses being substances, nonliving or living, which it has never been feasible to secure in the pure state and which are only recognizable by their injurious action, may, remaining invisible, enter the nuclei or act merely at the surface of the nucleus, on the cytoplasm or on the cell membrane. At present one cannot say which. No extraneous material has been detected within the injured nuclei. It is true that the nuclei are sometimes swollen, indicating an entrance of fluid. Some kinds of nuclei are more prone to do this than others, but one does not know what the fluid is. It may contain virus just as watery filtrates contain virus.

Evidently, therefore, until facts to the contrary are presented, it is logical to look to the normal contents of the nuclei for the material giving rise to the inclusions. In all nuclei, there is some acidophilic and some basophilic material, though the basophilic material predominates. Under the influence of the virus, the former is greatly increased in amount and concentrated in the central parts of the nuclei, while the latter is marginated on the nuclear membrane and is decreased in amount, finally disappearing entirely. This could be explained on the basis of a change in hydrogen ion concentration, but of such a change

one has no evidence. The increase in acidophilic (in reality basic) material might also be due to either increased formation or unmodified formation coupled with decreased elimination; but again one has no measurements to go on.

The intranuclear inclusions in several other virus diseases seem to be formed in much the same way as those of herpes and virus III, but the details of the process remain to be ascertained. Further detailed comparisons, under controlled conditions, will be required before the exact degree of specificity of the inclusions for the action of individual viruses can be measured.

When, finally, one learns how the viruses injure and kill, just as one knows the pharmacologic action of a few substances, it will presumably be possible to produce intranuclear inclusions experimentally by other agents than viruses. If this production of typical intranuclear inclusions should even be realized by purposefully altering the activity of cells, it is possible that a virus will at the same time have been created, but this would not necessarily be so. For the present it seems to me than one must hold an open mind. As I have insisted elsewhere,[13] the presence of intranuclear inclusions in unknown conditions should not be taken at face value as indicating the action of some filtrable virus. This point of view differs from that of Cole and Kuttner,[3] who, in the case of nuclear changes like those occurring in herpes simplex, assume a virus to be present unless its absence can be demonstrated.

SUMMARY

The comparison of inclusions caused by herpes and virus III in the testicles of rabbits under controlled conditions forty-eight hours after inoculation shows that:

1. The herpetic inclusions are more finely granular and less compact than the virus III inclusions.

2. The clear halo separating the herpetic inclusions from the nuclear membranes is narrower than in the case of the virus III inclusions.

3. The herpetic inclusions, being less dense, are tinged more lightly when the Feulgen reaction is applied than the virus III inclusions, though both usually give a negative reaction. A few fine particles are occasionally visible intensely colored by this test in the midst of the ground substance of the inclusions, particularly in those produced by virus III.

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13. Cowdry, E. V., and Scott, G. H.: A Comparison of Certain Intranuclear Inclusions Found in the Livers of Dogs with the Inclusions Caused by Virus III, Arch. Path. **9**:1184, 1930.

4. Both types of inclusions may occasionally exhibit a basophilia, either in a diffuse way of the ground substance of the inclusions or of fine particles embedded in them. This basophilia is not necessarily indicative of the presence of virus. The diffuse and punctate basophilias seem to correspond respectively with the light coloration of ground substance and the intense coloration of fine particles obtained in it by the employment of the Feulgen reaction.

5. Both types of inclusions in rare instances contain a few chromophobic vacuoles. This is particularly noticeable in virus III inclusions.

6. Both types of inclusions are equally resistant to solvents contained in fixatives employed in the preservation of tissues.

ADDISON'S DISEASE ASSOCIATED WITH CONGENITAL ABSENCE OF THE SUPRARENAL GLANDS*

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Thomas Addison[1] in 1849 first described the symptom complex which today bears his name. His description in 1855 of the characteristic features of the morbid state, namely, anemia, general languor and debility, remarkable feebleness of the heart action, irritability of the stomach and a peculiar change of color in the skin, occurring in connection with a diseased condition of the suprarenal capsules, remains complete. In the eleven cases reported by him the lesions found in the suprarenal glands were as follows: tuberculosis, six; cancer, four, and atrophy, one.

The suprarenal glands were discovered by Eustachius[2] in 1563. The oldest record of an illness which might have been Addison's disease was reported by Maranon.[3] This writer found an account of the illness of a young priest, which was recorded in the "Historia primitivia y exacto monasterio del Escorial." The priest's illness occurred in the years from 1554 to 1557 and dated from a fright incurred during a storm when lightning struck the monastery. The illness was one of melancholia and emotional instability, the color of the skin changing to a sad pallor. The patient lingered along, from bad to worse, and finally died after an illness that lasted three years.

Wilks[4] reviewed thirty-three instances of this condition, including five of Addison's original cases. Although he did not recognize the nature of the lesion in the suprarenal glands, there is little doubt from his description that they were all tuberculous.

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* From the Department of Pathology, Albany Hospital.

1. Addison, Thomas: Anemia, Disease of the Suprarenal Capsules, London M. Gaz. **43**:517, 1849; On the Constitutional and Local Effects of Disease of the Suprarenals, London, S. Highly, 1855.

2. Eustachius, quoted by Garrison, F. H.: History of Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1917.

3. Maranon, G.: Siglo méd. **70**:605, 1922; abstr., J. A. M. A. **80**:881, 1923.

4. Wilks, Samuel: On Diseases of the Suprarenal Capsule or Morbus addisonii, Guy's Hosp. Rep. **8**:1, 1862; Cases of Suprarenal Disease with Remarks, ibid. **11**:23, 1865. Wilks, Samuel, and Daldy, T. M.: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules in "A Collection of the Published Writings of Thomas Addison," London, The New Sydenham Society, 1868.

Barlow [5] reported a case in a woman, 42 years old, who died showing the classic addisonian syndrome. At necropsy, extreme atrophy of both suprarenal bodies was found. The atrophy was so marked that the suprarenal glands were not discovered until the abdominal organs had been removed from the body and a careful dissection made. In one of the kidneys was a gummatous lesion, but Barlow did not associate this with the atrophy of the glands. He mentioned Legg, Godhart, Eastes, and Davy as having described similar cases. Coupland [6] reported a case of Addison's disease with necrospy, in which there was no trace of the right suprarenal and in which the left gland was about one third the normal size. At that time, he was able to find five similar cases reported in the literature, one with entire absence of both suprarenals.

Lewin [7] made an extremely comprehensive review of the literature to 1892. In his first report he cited 683 cases of Addison's disease. In two of these there was complete absence of both suprarenal glands; in four cases the right gland, and in two the left gland could not be found. In the first series were twenty-three cases of Addison's disease in which both glands were markedly atrophied. In his second report of three hundred and ninety-two was one case of Addison's disease with complete absence of both suprarenal glands, three with the right and one with the left suprarenal gland absent. In the second report were ten cases with both suprarenal glands markedly atrophied.

Phillips [8] reported one case of Addison's disease with atrophy of the suprarenal gland as the essential lesion. In the literature at that time he found reports of fourteen instances of simple atrophy of the suprarenal glands associated with symptoms of Addison's disease. He stated that his case was the first reported in this country, and that in three cases the glands had been entirely absent.

Spencer [9] reported a case of Addison's disease in which at necropsy entire absence of the suprarenal glands was noted.

Chvostek [10] described a young man in whom Addison's disease developed following a bilateral perinephric infection which resulted in total destruction of the suprarenal glands with death in a short time.

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5. Barlow, Thomas: Simple Atrophy of the Suprarenal Capsule and Gumma of the Kidney in a Case of Addison's Disease, Tr. Path. Soc. London **36**:433, 1885.

6. Coupland, Sidney: Atrophy of Adrenals with Addison's Disease, Tr. Path. Soc. London **36**:423, 1885.

7. Lewin, G.: Ueber Morbus addisonii, Charité-Ann. **17**:536, 1892.

8. Phillips, Carlin: Addison's Disease with Simple Atrophy of the Adrenal Bodies, J. Exper. Med. **4**:581, 1899.

9. Spencer, cited by Hektoen and Riesman: Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1901.

10. Chvostek, cited by Tieken, T.: Addison's Disease: Report of a Case with Acute Onset Terminating in Rapid Improvement and Complete Recovery, Am. J. M. Sc. **152**:422, 1916.

Bittorf [11] collected from the literature reports of forty-seven cases of Addison's disease in which necropsy revealed atrophy of the suprarenal glands. To this series, he added five of his own, three coming to necropsy with the same condition. In a study of the suprarenal glands, three showed involvement of the cortex only, the remainder, involvement of the whole organ. In all but one case there was present a hyperplastic condition of the lymphoid tissues. He believed, with Löffler [12] that there is a relation between status thymicolymphaticus and Addison's disease.

Swan and Bortree [13] reported seven cases of Addison's disease. Tuberculosis of the suprarenal glands was present in all three cases. They found that the death rate from Addison's disease was 0.4 per hundred thousand population for the registration area of the United States. Rowntree [14] gave the death rate for the British Isles as 0.6 per hundred thousand and of Japan as 0.04 per hundred thousand population.

Mohler [15] and Fleming [16] each reported a case of Addison's disease in which necropsy showed gross absence of suprarenal tissue. However, microscopic examination of the fatty tissue in the area where the suprarenal glands are normally found revealed small islands of chromaffin tissue.

Pappenheimer [17] published a study of hypoplasia of the suprarenal glands in association with malformations of the brain. In the older references, the statement was frequently made that in cases of anencephaly and kindred malformations the suprarenal glands may be entirely wanting. In concluding he made the statement that the small size of the suprarenal gland is due wholly to the failure of development of the fetal zone of the cortex, and suggested that it is this transitory cortical tissue which is in some way correlated with the normal development of the brain. Kohn [18] stated that severe malformations or absence of suprarenal glands occur almost solely in monsters, especially anencephaly.

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11. Bittorf, A.: Addison's Disease of Suprarenals, München. med. Wchnschr. **73**:1928, 1926.

12. Löffler, W.: Beitrag zur Kenntnis der Addison'schen Krankheit, Ztschr. f. klin. Med. **90**:265, 1920.

13. Swan, W. H., and Bortree, L. W.: Addison's Disease with Report of Cases, Boston M. & S. J. **194**:712, 1926.

14. Rowntree, L. G., and Snell, A. M.: Clinical Experience with Addison's Disease, Ann. Int. Med. **3**:6, 1929.

15. Mohler, H. K.: Addison's Disease: Discussion of Symptoms; Report of a Case with Autopsy Findings, M. Clin. North America **4**:1255, 1921.

16. Fleming, C. M.: Fatal Case of Addison's Disease, Brit. M. J. **1**:951, 1922.

17. Pappenheimer, A. M.: Hypoplasia of Adrenals in Anencephaly, Proc. New Path. u. path. Anat. **40**: 387, 1927.

18. Kohn, A.: Anencephalie und Nebenniere, Arch. f. mikr. Anat. u. Entwicklungsm. **102**:113, 1924.

Conybeare [19] collected a series of cases of Addison's disease which occurred between the years 1904 and 1923 at Guy's Hospital, all with necropsy. Of the twenty-nine patients, twenty were males and nine, females, and in more than half death occurred between the ages of 20 and 40. In twenty-two the suprarenal glands were found tuberculous, and in several they appeared to be in a condition of simple atrophy. In one case of simple atrophy, the condition was so extreme that complete and careful search failed to reveal any evidence of either gland. The cases with atrophy of the suprarenal glands showed remarkable freedom from tuberculous lesions and in only two of the seven cases was there old tuberculous scarring in the lungs and in none any evidence of active or recent tubercle.

Wahl [20] cited a case of Addison's disease in which there was a condition of the suprarenal glands resembling atrophy, but which he believed to be a perverted and prolonged embryonic process.

Harbitz [21] stated that in twenty-five years he had examined twenty-two cases of Addison's disease, and had always found extensive destructive lesions in both suprarenal glands. Tuberculous lesions were present in twenty, and severe and chronic inflammation and atrophy in two cases. Krause [22] associated atrophy of the suprarenal glands in Addison's disease with a pathologic condition in the hypophysis.

Voigt [23] reported the case of a woman, 43 years old, who died following one year of progressive weakness, loss of weight, vertigo and increasing pigmentation of the skin. The Wassermann reaction of the blood was strongly positive. The clinical diagnosis was Addison's disease. At autopsy, in spite of careful search in the region of the kidney and the entire abdomen, no suprarenal tissue was found on either side. Suprarenal arteries could not be demonstrated. A definite status lymphaticus was present.

Wakefield and Smith [24] reported three cases of Addison's disease with necropsy on two of the patients. One showed caseous degeneration of both suprarenal glands. The other showed two types of lesions;

19. Conybeare, J. J., and Millis, G. C.: Observation of Twenty-Nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904-1923, Guy's Hosp. Rep. **74**:369, 1924.

20. Wahl, H. R.: Malformation of Adrenal Glands with the Clinical Picture of Addison's Disease, M. Clin. North America **7**:1357, 1924.

21. Harbitz, F.: The Suprarenals in Addison's Disease, Norsk Mag. f. Laegevidensk. **87**:371, 1926; abstr., J. A. M. A. **87**:290, 1926.

22. Krause, E. J.: Zur Pathologie des Morbus addisonii, Beitr. z. path. Anat. u. z. allg. Path. **78**:282, 1927.

23. Voigt, W.: Angeborenes Fehlen beider Nebennieren, Centralbl. f. allg. Pathol. u. path. Anat. **40**:387, 1927.

24. Wakefield, E. G., and Smith, E. E.: Addison's Disease, Suprarenalopathies, Sclerosis of the Glands of Internal Secretion, Am. J. M. Sc. **174**:343, 1927.

one gland could not be found, and the other showed an acute process superimposed on an old sclerosis. They believed that the gland which could not be found was destroyed by the same process as was present in the other gland. The family history is interesting in that seven males in four generations had had bronzing of the skin from birth. It suggests a congenital lack of chromaffin tissue and perhaps a similar cause for the absence of the one gland.

Kovacs [25] reported eight cases of Addison's disease. In four, tuberculous degeneration of both suprarenal glands was found, and in the other four the glands were markedly atrophied. In one case, the atrophy was of the so-called idiopathic type and in the other three, the suprarenal vessels were thrombosed. He said nothing about the embryonal development of the suprarenal glands or the possibility of a congenital absence of these glands.

Keifer [26] reported the case of a woman, 58 years old, who died of Addison's disease. Necropsy disclosed a high grade of atrophy of the suprarenal glands with some fibrous regeneration.

Medlar [27] reported two cases of Addison's disease, one with status thymicolymphaticus, in which the suprarenal glands were small and firm. Microscopic examination showed marked atrophy of the cortex and large areas with no suprarenal parenchyma. Marked fibrosis of the cortex and medulla and lymphocytic infiltration throughout both organs were present. In the second case with generalized lymphoid hyperplasia, no suprarenal glands could be found on gross examination and no accessory suprarenal tissue around or in the kidneys, along the ureters or in the pelvic tissue. A section of the tissue in the region where the suprarenal glands are normally found showed here and there small clumps of cortical or of medullary tissue in which there was extensive lymphocytic infiltration. The areas containing suprarenal parenchyma showed some of the parenchymal cells necrotic and invaded by mononuclear and polymorphonuclear leukocytes. Both of these cases were associated with lymphoid hyperplasia, and Medlar was of the opinion that "Addison's syndrome is produced only in cases of extreme suprarenal insufficiency and that status thymicolymphaticus is but an indication of adrenal insufficiency."

Brenner [28] reported five cases of Addison's disease in which atrophy played the important rôle. In his fifth case, no suprarenal tissue was

25. Kovacs, W.: Zur Nebennierenpathologie, Beitr. z. path. Anat. u. z. allg. Path. **79**:213, 1928.

26. Keifer, Hans: Addisonsche Erkrankung infolge chronischer Nebennieren Dystrophie mit adenomartigen Regeneraten, Arch. f. path. Anat. **265**:472, 1927.

27. Medlar, E. M.: A Report of Two Cases of Essential Adrenal Insufficiency (Addison's Disease), Am. J. Path. **3**:135, 1927.

28. Brenner, O.: Atrophy of Cortex of the Suprarenals, Quart. J. Med. **22**:121, 1928.

found in spite of prolonged search. He suggested that the pathologic process is a necrosis of cortical cells caused by some unknown toxin which has a special affinity for them. The few cortical cells left after the primary damage are probably overworked and the subsequent degeneration is possibly due to exhaustion atrophy.

Lawrence and Rowe [29] reported nine cases of Addison's disease. In six cases, no necropsy was performed, but in the others the suprarenal lesions were as follows: atrophy one, tuberculosis one and carcinoma one.

Karsner [30] pointed out that atrophy of the suprarenal glands may occur in old age, and he found one instance of Addison's disease with atrophy of the suprarenal glands as the essential feature.

Philpott [31] reviewed 2,550 cases in which autopsy was performed and found fourteen which could be classified as Addison's disease. The suprarenal lesions in these were as follows: tuberculosis seven, metastatic carcinoma four, mycosis fungoides one, simple atrophy one and amyloidosis one. He went on to discuss the case of amyloidosis and failed to mention further that of simple atrophy.

Petter [32] made a brief review of the literature and found one hundred and twenty-one cases of Addison's disease reported showing pathologic evidence in the suprarenal glands as follows: atrophy twenty-two, tuberculosis eighty-nine, carcinoma seven, mycosis fungoides one and amyloidosis, one. According to his report, he found no cases in which the suprarenal glands could not be found.

Barker [33] reviewed the literature of Addison's disease to 1929 and added twenty-eight cases collected in the previous eighteen years at the Mayo Clinic. In one, complete absence of suprarenal tissue was noted. In another, one suprarenal gland was a solid calcified mass about the size of a normal gland, and the only remains of the other gland were two small nodules of rather dark colored tissue, each about 5 mm. in diameter. Histologically, these consisted of deeply pigmented medullary tissue with a narrow margin of normal sized but deeply pigmented cortical cells.

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29. Lawrence, C. H., and Rowe, A. W.: Studies of the Endocrine Glands, Endocrinology **13**:1, 1929.

30. Karsner, H. T.: Text Book of Human Pathology, Philadelphia, J. B. Lippincott Company, 1926.

31. Philpott, N. W.: Addison's Disease in Association with Amyloidosis, Ann. Int. Med. **1**:613, 1927-1928.

32. Petter, C. K.: Addison's Disease, with Report of Two Cases and Review of the Literature, Minnesota Med. **12**:194, 1929.

33. Barker, N. W.: The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, Arch. Path. **8**:433, 1929.

Debarge [34] discussed the case of a previously healthy man, aged 90, who died apparently of bronchopneumonia. Autopsy disclosed, in addition to the pneumonia, complete absence of the right suprarenal gland. There was none on the left in the normal place, but a small mass was found in the retroperitoneal tissue near the tail of the pancreas. Serial sections of this mass revealed nothing which could be identified as suprarenal tissue, but there was considerable tuberculous caseation. The right kidney contained a tumor mass which almost doubled its normal size. It consisted microscopically of fibrous tissue, necrotic material and typical suprarenal cortical cells. Chromaffin cells could not be identified by staining. The tumor cells showed malignant changes. The author concluded in his second paper that prolonged life is possible with an infinitesimal number of suprarenal cortical cells, and that a strictly cortical malignant hypernephroma can reproduce exactly the function of normal suprarenal cortical cells.

REPORT OF CASE

The case here described is from the medical service of Dr. Thomas Ordway, of the Albany Hospital, who permitted me to use the clinical record; Dr. F. Constance Stewart supplied the clinical history.

History.—A white woman, aged 35, unmarried, entered the Albany Hospital in a state of marked asthenia. She gave a history of progressive weakness for a period of five months. This had been intensified during the few days before admission owing to the increased nausea and vomiting that had developed.

Because of the extreme illness of the patient and the lack of any family from whom to obtain an adequate history, little information as to the previous events in her life was ascertained. She had lived with her parents until they died a few years previously. Recently she had attempted light housekeeping.

Examination.—When one first saw the patient, one was impressed not only by her extreme prostration, but also by the uniform brown pigmentation of her skin. This was most marked on the exposed surfaces of the face, neck, hands and arms. She appeared as one recently returned from a vacation by the seaside, but she had not had prolonged exposure to the sun's rays since making a tour through the southwestern states the preceding winter. The mucous membranes, which were slightly cyanotic, showed no pigmentation.

In addition to the asthenia and pigmentation, the most marked physical abnormalities were the weakness of the heart sounds and the very low blood pressure. When the patient was first seen, no sounds could be heard by the auscultatory method of obtaining the blood pressure. An effort was made to raise the blood pressure by injections of epinephrine hydrochloride, but at no time did the systolic pressure get above 76 mm. of mercury, or the diastolic above 50 mm. She complained greatly of soreness and stiffness in various parts of the body where the injections were given. Because of this low pressure, all attempts to obtain blood for chemical and serologic studies were unsuccessful.

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34. Debarge, Claire: Hypernephroma with Suprarenal Aplasia, J. de physiol. et de path. gén. **26**:639, 1928; abstr., Arch. Path. **7**:1115, 1929.

The urinalysis showed a slight trace of albumin with a rare leukocyte and an occasional cast. The hemoglobin was 93 per cent (Sahli); the red blood cells, 4,590,000; the white blood cells, 3,320, with a differential count of 65 per cent neutrophils and 35 per cent lymphocytes. The temperature ranged between 95.5 and 101 F. The pulse rate fluctuated between 70 and 130, and the respirations varied from 20 to 30 per minute.

After the fluids had been forced for a few days, first by proctoclysis and then by mouth, the patient improved so that a careful roentgenographic study of the lungs and the gastro-intestinal tract could be made. No pathologic changes were revealed to aid in the diagnosis. The heart appeared smaller in size than the usual normal.

Although the patient had shown a few signs of improvement, she suddenly became much weaker on the twelfth day after admission and died.

Diagnosis.—A clinical diagnosis of Addison's disease was made. Anatomic diagnoses: Addison's disease, congenital aplasia of the suprarenal glands and edema of the lungs. Microscopic diagnosis: congenital aplasia of the suprarenal glands, with ectopic foci of suprarenal cortical tissue, acute congestion of the lungs, congestion of the spleen and cutaneous melanosis.

Necropsy.—Necropsy was performed seven and one-half hours after death by Dr. V. C. Jacobsen and Dr. E. H. Crosby. The body was that of a fairly well developed, poorly nourished white woman, 64 inches (162.6 cm.) long. Rigor mortis and postmortem lividity were present, with moderate edema of the feet and ankles. There was a marked brownish tinge of the skin over the face and neck, and spots of brownish pigment over the chest and abdomen.

The right inguinal glands were enlarged. The hair was brown, turning gray. Ears, nose and mouth were normal. A small conjunctival hemorrhage was present in the left eye.

The abdominal fat appeared normal. The mesenteric lymph nodes were slightly enlarged, and the retroperitoneal lymph nodes were about 1.5 cm. in diameter and were hard, but not caseous.

The pleural and pericardial cavities were normal. The mediastinal glands were not enlarged.

The heart was in systole. It was somewhat reduced in size. The coronary vessels were not palpable.

The lungs were moderately edematous throughout. The hilic lymph glands were of normal size.

The spleen weighed 145 Gm. It was slate blue externally and soft. On section, the lymphoid follicles were prominent.

The gastro-intestinal tract, pancreas and liver were normal.

The gallbladder was dilated and its wall thickened. Three large stones could be felt in its cavity and one in the cystic duct. The external surface was streaked with red, especially in the fundus. On section, the wall was thickened and firm. It was filled with a mucous, watery fluid. Three large mulberry stones, 2 cm. in diameter, lay free in the lumen. The gall ducts were patent.

The kidneys weighed 110 Gm. each. They were of similar appearance. The capsule stripped with slight difficulty and left a smooth surface. On section, fine whitish streaks were seen throughout the cortex. The cortex averaged from 4 to 5 mm. in thickness, and the general topography was normal. The pelvis and ureters were normal.

The urinary bladder was contracted and empty.

The uterus was small and firm, the tubes normal. The ovaries were small and, on section, contained several cysts filled with a clear yellow fluid.

The aorta revealed a few yellowish atheromatous patches in the abdominal portion.

Search was made for the suprarenal glands in situ, but they could not be found after close inspection of the abdomen and the retroperitoneal tissues. The kidneys, the perirenal fat and the surrounding tissues were removed en masse. The perirenal tissue was carefully dissected and explored. Nothing resembling suprarenal tissue could be discovered. Several enlarged lymph nodes were encountered. All the loose retroperitoneal tissue was therefore put in Zenker's fluid for microscopic

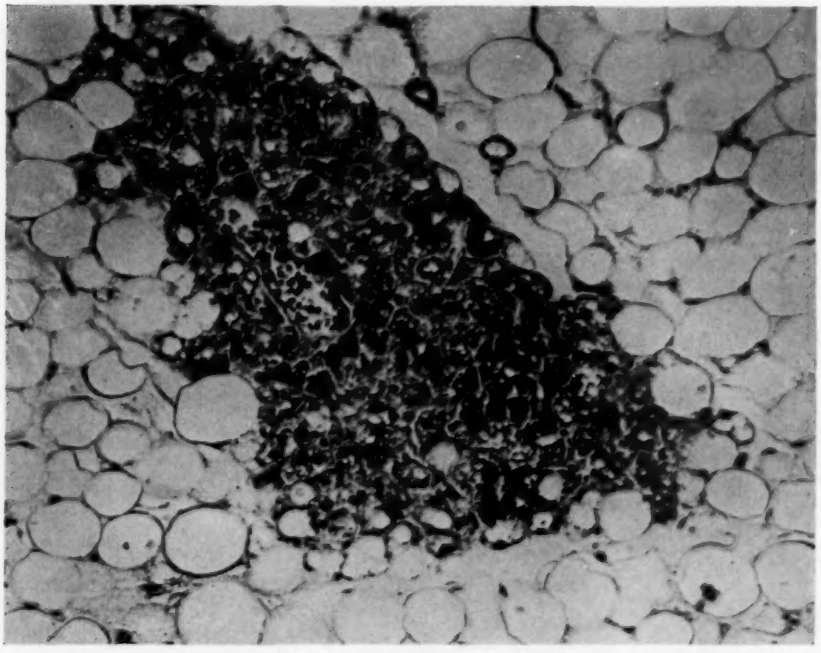

Fig. 1.—Photomicrograph of a section taken from the retroperitoneal tissues about the superior poles of the kidneys, showing a compact islet of cells which much resembles the zona reticularis of the suprarenal cortex. Near the center is a nutrient vessel.

study. Nothing was seen on any of the viscera, suggestive of aberrant suprarenal tissue.

Microscopic Examination.—The lungs presented acute congestion, edema, slight hemosiderin pigmentation and catarrhal bronchitis. The spleen showed acute congestion and an increased number of polymorphonuclear leukocytes in the blood spaces. The gastro-intestinal tract showed some engorgement of vessels in the large intestines. The pancreas and the liver were normal. In the gallbladder there were chronic inflammatory changes. Melanin was present in moderate amount in the malphigian layer of the skin. In the kidneys were cortical areas of round cell infiltration. A few glomeruli showed capillary sclerosis.

In two of the sections of the retroperitoneal tissues, islands of cells were found such as the one illustrated in figure 1. These islands were composed of compact collections of cells which had many points of resemblance to those of the suprarenal cortex: the same fine granulation, deeply eosinophilic staining of the cytoplasm, lipoid and fat droplets. In addition, some of them contained a pale brownish-yellow pigment suggesting that of the zona reticularis of a suprarenal gland. These cell aggregates were not encapsulated, but a nutrient vessel occupied a prominent position in each.

COMMENT

Lying as they do, surrounded by fat, the question arises, are these cell groups exhausted fat cells? A conclusive answer is impossible, but in their pigmentation and staining properties they more closely resemble suprarenal cortex than exhausted or fetal fat cells. No rests of the appearance of medullary tissue were found, but the chromaffin tissue of suprarenal origin is not so characteristic as to be identified with certainty. The patient was undernourished but not emaciated, and fat exhaustion is usually seen only in the most cachectic persons. It is my opinion that these cell aggregates in the perirenal fat represent suprarenal cortical tissue.

Loeper and Ollivier [35] reported the case of a woman, 31 years old, who died showing the classic symptoms of Addison's disease. At necropsy, both suprarenal glands were found involved in a fatty metamorphosis in which no inflammatory or infectious process could be demonstrated. Figure 2 is a copy of a picture in their article showing the infiltration of fat cells into a portion of a suprarenal gland. It can be safely said that at some time in their patient's life suprarenal glands of normal contour probably existed. I believe that in the case here reported suprarenal glands as such were never formed, but that the scanty amount of tissue nevertheless was sufficient to maintain life for thirty-five years.

It has been shown by Webber [36] that when the suprarenal glands are apparently absent, careful search will often disclose the tissue in other situations, on the liver, on the kidneys or somewhere along the alimentary tract. This heterotopia of the suprarenal glands was emphasized by Miloslavich,[37] who collected and reported fourteen cases of heterotopia of the suprarenal glands.

35. Loeper, M., and Ollivier, J.: Metamorphose adipense des deux capsules surrenales avec mélanodermie, Bull. et mém. Soc. méd. d. hôp de Paris, **50**:312, 1926.

36. Webber, C. V.: Heterotopia of Adrenals in Liver and Kidneys, Am. J. M. Sc. **169**:696, 1925.

37. Miloslavich, L. H.: Ueber Bildungsanomalien der Nebenniere, Virchows Arch. f. path. Anat. **218**:131, 1914.

The factors leading to congenital anomalies of the suprarenal glands can be better understood if the embryology of these bodies is reviewed briefly.

The cortex and the medulla have entirely different developmental histories.[38] In the lower vertebrates (fishes), the two parts of the gland continue separate throughout life. In the ascending mammalian scale, the two parts become more and more closely united until in mammals they form a single organ. The cortex develops from mesoderm, first appearing in embryos of from about 5 to 6 mm.

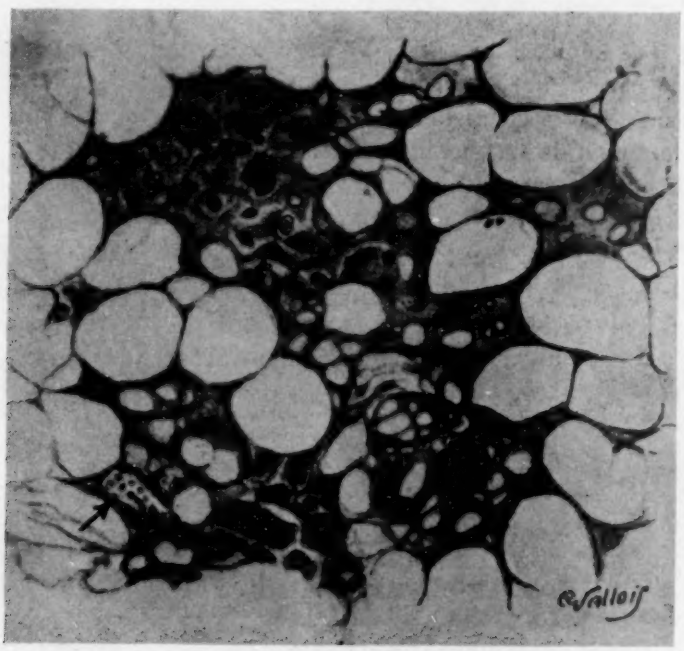

Fig. 2.—Infiltration of fat cells into the suprarenal gland. The arrow points to a blood vessel. There is a marked resemblance to the islet in figure 1. The picture is taken from Loeper and Ollivier (Bull. et mém. Soc. méd. d. hôp. de Paris **50**:312 [Feb.] 1926).

At about the level of the cephalic third of the mesonephros, the mesothelium sends outgrowths into the mesenchyme. These outgrowths soon lose their connection with the main mass of mesothelium and constitute the anlage of the suprarenal cortex. The medulla has an entirely independent origin, being derived from ectoderm as part of the peripheral sympathetic nervous system. The cells of some of the sympathetic ganglions differentiate into sympathoblasts and pheochromoblasts,

38. Bailey, F. R.: Textbook of Histology, ed. 3, New York, William Wood & Company, 1910.

which give rise to the sympathetic cells and the chromaffin cells, respectively. These cells soon separate from their ganglions of origin and come to be first near, then within, the developing cortex, thus forming the medulla.

From the development of the suprarenal gland, it is apparent that a great deal depends on the two anlagen from the ectoderm and the mesoderm being brought together and surrounded by a capsule. Let us suppose that the union failed to take place. The cortex and the medulla could lie near each other, but distinctly separate. Or they might wander far from their normal resting places and come to lie in widely removed regions. The same influences that govern such union might conceivably create a much fragmented suprarenal apparatus. These fragments might be very small but sufficient to sustain life up to a certain age after which signs of insufficiency would develop with the typical Addison's syndrome. The many insults of disease to which the human body is subjected in the struggle to adulthood might cause degenerative changes in such suprarenal rests or lead to their ultimate exhaustion. Graham [39] pointed out that extensive necrotic changes may occur in the suprarenal cortex in diphtheria, scarlet fever, measles and other infectious conditions. He mentioned a fatal case of measles in which the suprarenal glands in a woman 35 years old showed complete necrosis of all three cortical zones, as well as of the medulla. It is true that a very small amount of suprarenal tissue is sufficient to sustain life, but exactly how much that is for a given age is not known. Also knowledge is in an unsettled state as to whether medulla or cortex or both layers can produce epinephrine.

It cannot be stated categorically that the retroperitoneal islands present in the case reported here were truly suprarenal tissue. I believe that they were, but the evidence as adduced is offered only for what it is worth. In the absence of definite suprarenal glands, some form of rest must have sustained life, in this instance, to the age of 35 years.

SUMMARY

Of all the diseases affecting the suprarenal glands, atrophy is one of the least common, and absence of these glands is rare. It is not known exactly how much suprarenal tissue is essential to life, but a very small amount often seems to be sufficient. It is not necessary for suprarenal tissue to be in the normal position; aberrant rests may be found almost anywhere within the abdomen.

The case of a woman who died at the age of 35 years is reported, in whom at necropsy no gross evidence of suprarenal tissue could be

39. Graham, G. S.: Toxic Lesions of the Adrenal Gland and Their Repair, J. M. Research **34**:241, 1916.

discovered. Microscopically, small islands of suprarenal cortex were found near the superior poles of the kidneys embedded in retroperitoneal fat.

It is evident that in cases such as this, the embryonic development of the suprarenal gland has been faulty, but that cortical and medullary tissue has existed in sufficient amount to sustain life for many years, finally to become exhausted, a condition resulting in typical Addison's disease and death.

RHEUMATIC PERICARDITIS WITH POLYPOID FORMATIONS *

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In the pericardium of a man with typical rheumatic heart disease, a peculiar polypoid mass was found. The patient, 27 years old, white, died of cardiac decompensation from rheumatic endocarditis of long standing, with mitral stenosis and regurgitation. The endocarditis followed two attacks of rheumatic fever. Although the patient was under observation most of the time, clinical evidence of pericarditis was never found.

Necropsy disclosed an old mitral and aortic valvulitis with calcification of the large irregular vegetations. Engrafted on this old process was a recent mitral, aortic and tricuspid endocarditis in the form of fine pearly nodules at the free margins of the valves. The left auricle and both ventricles were greatly hypertrophied, and the left auricle, right ventricle and, most of all, the right auricle were dilated. The heart, with the pericardium, weighed 1,400 Gm.

The unusual features were in the pericardium (fig. 1). There were adhesions between the pericardial layers, in most places fibrinous and easily broken, but in the region of the interventricular septum anteriorly the two layers were firmly bound together. From about 75 to 100 cc. of cloudy, slightly brownish fluid was found in the sac. Both layers were covered by shaggy fibrinous material easily stripped off. The color of the pericardium was chocolate brown.

At the reflection of the parietal pericardium from the right auricle posteriorly hung a large hydatidiform mass, 7 cm. long, 8.5 cm. wide and about 2.5 cm. thick. The distal two thirds of this mass was made up of several dozen bluish, polypoid bodies from 4 to 15 mm. in diameter, a few of them solid but most of them filled with blood in various stages of inspissation. In some, the contents were thick and chocolate brown. From the posterior part of the mass hung a loop of firm tissue, 1.5 mm. thick; from the lowest point of this loop, a thinner strand of tissue, 1 mm. thick and 4 cm. long, descended, and from its tip hung, like a pendant, a flat triangular solid body 17 by 10 by 5 mm. A smaller pendant hung by a fine threat from the extreme left of the large mass. Over the surface of the auricle and underneath the auricular appendage there were tiny brownish projections, from 0.5 to 3 mm. in length, usually solid but occasionally cystic, the contents of the cysts being old

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* From the Department of Pathology and Bacteriology, University of Illinois, College of Medicine.

blood. When the adhesions anteriorly were removed there were seen isolated blood-containing cysts similar to those in the large mass. On the anterior surface of the left ventricle there was a single, button-like projection surmounted by several tiny polypoid masses.

Microscopically, the polypoid bodies were cysts with walls of varying thickness, lined by a single layer of flattened cells and filled with erythrocytes (fig. 2). The solid bodies showed all the stages from

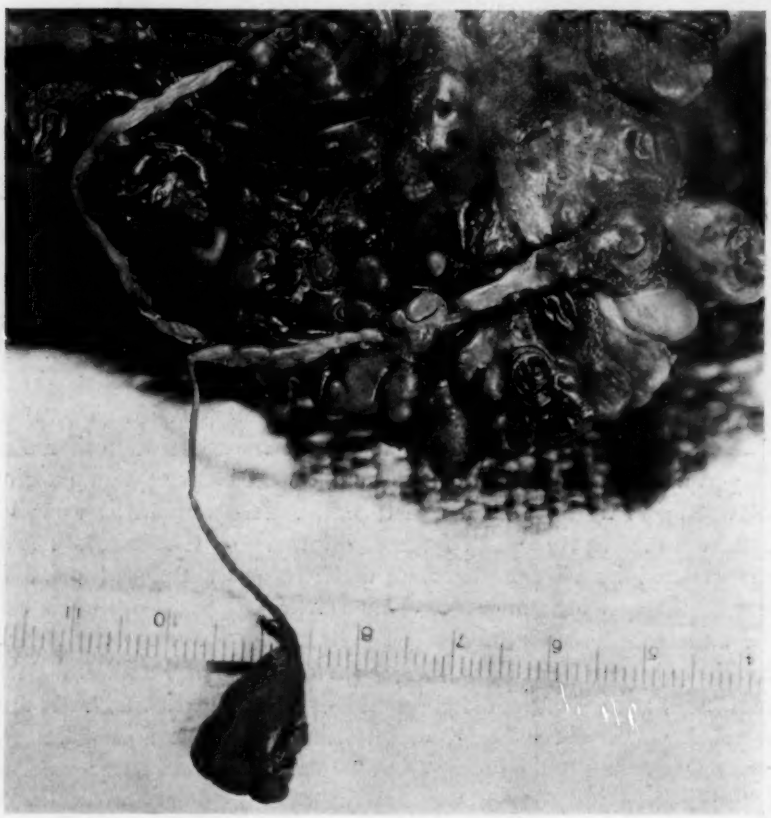

Fig. 1.—The under surface of the polypoid mass.

only partly organized thrombotic masses to old hyaline connective tissue. In the walls of the cysts were many macrophages filled with blood pigment.

Between the cysts were dense infiltrations principally of large pale cells of the histiocyte or macrophage type but containing also lymphocytes and a few plasma cells. The cells were often large, with two or three nuclei. Frequently these accumulations were nodular and near blood vessels, giving the appearance of Aschoff nodules, much larger,

however, than those ordinarily found in the myocardium. Several of the nodules had necrotic centers.

The free surface of the epicardium and often also the external surfaces of the polypoid masses were covered by clumps of fibrin, most of them fused into hyaline masses. But in addition to fibrin there were large numbers of red blood corpuscles, some monocytes and lymphocytes. The granulocytes were few. The fibrin could at times be seen to bridge over two masses of old granulation tissue. In such cases, a cystlike space was left filled with red blood cells. When the fibrin was adherent

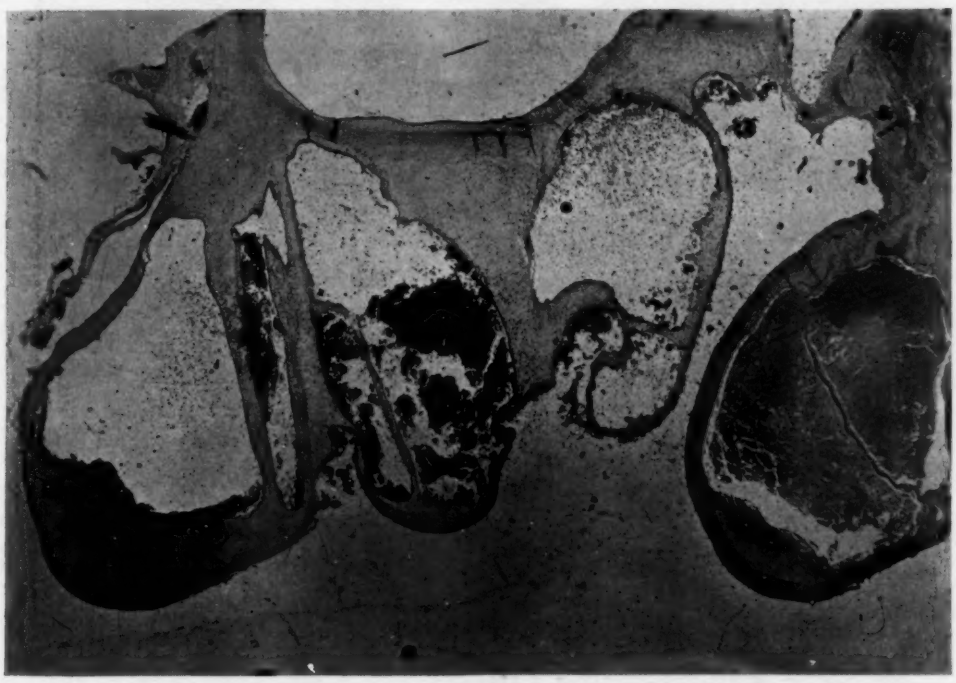

Fig. 2.—Section through a group of larger polypi. Most of the blood has fallen out of the large cysts. On the right is one of the solid bodies. Hemalum and eosin.

to the pericardium or to the older granulation tissue, the endothelium was destroyed, but sometimes endothelial cells, apparently from the periphery, covered part of these newer fibrinous bridges; in a few cases, complete endothelium-lined cysts were thus formed, enclosing the hemorrhagic exudate.

COMMENT

In a healing or healed pericarditis there are often found endothelium-lined spaces, small or large; in the common large pericardial plaques, they

are frequent. Occasionally these spaces become larger, forming small cysts. In one case, Lauche [1] found numerous cysts, ranging in size to that of a pea, over the surface of the right ventricle. The explanation for these spaces and for Lauche's cysts has been that the endothelium-covered, organized fibrinous masses in a fibrinous pericarditis have fused at their tips, enclosing small spaces. With the continuous motion of the heart, these spaces gradually became larger. This explanation can, I think, be substantiated in my case.

The only feature left to explain is the blood in the cysts. Lauche's cysts were filled with clear fluid. If, however, the inflammation had been hemorrhagic, blood would have been enclosed in the cystlike spaces and would gradually have undergone organization. That, in the present case, one has to deal with a hemorrhagic inflammation is indicated by the recent recurrent hemorrhagic pericarditis and by the chocolate brown color of the pericardium and the fluid in the pericardial sac. Thorel [2] pointed out that rheumatic pericarditis is often hemorrhagic.

Grossly, the mass in the pericardium resembles somewhat a neoplasm. Timme [3] reported a much smaller mass in the pericardium as a cavernous hemangioma. It is interesting that in his case, too, mitral stenosis and insufficiency were present. Histologically, the "structure showed a collection of dilated blood vessels. . . . The walls of these vessels contained no muscle or elastic tissue whatever; they were fibrous in character. The contents of the vessels were typical blood clots." Except for the cellular infiltrate between the cysts in my case, the two cases are much alike. Perhaps Timme's hemangioma, too, was the end-result of an old pericarditis in which inflammation had long since subsided.

The specificity of the Aschoff nodule or its histogenesis cannot be discussed here; but the presence in the pericardium of cellular aggregations in close relation to blood vessels, made up of large cells resembling macrophages, and associated with definite clinical and pathologic evidence of rheumatic endocarditis may be taken as indications of the rheumatic nature of the pericarditis.

SUMMARY

A hydatidiform mass in the pericardium is reported, which is apparently unique. It is considered to be a peculiar result of the healing of rheumatic hemorrhagic pericarditis.

1. Lauche, A.: Cystenbildung auf der Oberflache des Herzens nach Pericarditis, Centralbl. f. allg. Path. u. path. Anat. **30**:321, 1919.

2. Thorel: Pathologie des Herzens, in Lubarsch und Ostertag: Ergebn. d. allg. Path. u. path. Anat. **17**:714, 1915.

3. Timme, A. R.: Cavernous Hemangioma of the Pericardium, Cleveland M. J. **14**:453, 1915.

PERIARTERITIS NODOSA*

REPORT OF A CASE

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ST. LOUIS

The literature of periarteritis nodosa has been reviewed by Gruber.[1] The case reported here, aside from the interest attaching to its clinical course, is important because the distribution of its vascular lesions suggests an explanation concerning the pathogenesis of the disease. The author is indebted to Dr. Leo Loeb for his advice in the study of this case.

CASE REPORT

History.—A white man, aged 67, entered Barnes Hospital on March 22, 1927, with the chief complaints of pain in the legs, inability to walk, jaundice and fever. His family history seemed irrelevant. He had had typhoid fever in youth. Since the age of 46, he had suffered from peptic ulcers which, however, could be well controlled by medication. He had had nocturia for four years and slight dyspnea on exertion for two years. He said that he had not had venereal infection.

In February, 1927, he began to experience tingling sensations and shooting pains in the ankles and feet, which were slightly swollen and could not be moved. He was unable to leave his bed. Two weeks later, his arms became similarly involved. Although there were never any definite joint pains, he was treated for five weeks before admission by hot packs and oil of wintergreen rubs, under the impression that the condition was arthritis. Two weeks after he became ill, definite jaundice with bile in the urine developed, but when I saw him the jaundice had disappeared.

Physical Examination.—Examination revealed a heavy-set man, deeply pigmented but sallow. His temperature was elevated, and the general picture was that of a severe infection. His expression was masklike, his eyes staring; he hiccuped at intervals and had a moderately severe cough, productive of a large amount of thin, greenish, sweet-smelling sputum. There was a questionable edema of the optic disks. The chest was emphysematous, and a few moist râles could be heard at both bases. The heart was enlarged. The sounds were distant, but no murmurs were heard. The blood pressure was 115 systolic and 70 diastolic. The abdomen was full and difficult to palpate. The liver was not felt; percussion indicated no enlargement. The hands were large and flat, with definite atrophy of the intrinsic muscles. There was a toe-drop and wrist-drop. All of the deep reflexes were absent, and no plantar response of any kind was present. He had hyperesthesia of both hands and feet.

The urine was cloudy and at one time was of a dark port wine color which did not change on exposure to light. There was no bile; the test for albumin was

* Submitted for publication, Feb. 11, 1930.

* From the Departments of Pathology and Internal Medicine, Washington University School of Medicine.

1. Gruber, G. B.: Zentralbl. f. Herzkrankh. u. Gefässkrankh. **9**:45, 1917.

4+; for sugar, negative. The excretion of phenolsulphonphthalein was 42 per cent in forty-five minutes. The nonprotein nitrogen of the blood was 33 mg., and the chlorides of the plasma, 470 mg. The carbon dioxide of the plasma was 59 per cent by volume. The count of red blood cells was 4,500,000; that of white blood cells, 25,000, with polymorphonuclears 87 per cent and eosinophils 2 per cent.

Course.—Under observation, the patient's condition became steadily worse. The temperature curve became definitely more septic in type. The leukocytes remained persistently high. Edema of the extremities, especially of the hand, increased with increasing inability to use them. Numerous blood cultures were negative both under aerobic and anaerobic conditions. After two transfusions, red blood cells appeared and persisted in the urine. The blood pressure shortly after admission rose to 160 systolic and 100 diastolic and in subsequent days continued to rise, slowly but rather steadily. Three weeks after admission, the patient suddenly became stuporous. His blood pressure rose to 200 systolic and 100 diastolic; the temperature began to fall; the pulse rate became more rapid; albumin and red cells increased in the urine; the nonprotein nitrogen rose to 95 mg., and the patient died.

Pathologic Examination.—The pathologic examination showed the body to be that of a well developed and fairly well nourished white man about 67 years of age. When the body was opened, no excess fluid was found in the cavities. The heart was enlarged, weighing 473 Gm. The heart muscle, on section, appeared normal, although a slight degree of coronary sclerosis was noted grossly. The endocardium was normal. A patent foramen ovalis was present. Microscopically, accumulations of small groups of lymphocytes were seen about some of the smaller blood vessels. Adhesions were present at the apices of both lungs, binding them to the chest wall. On section, frothy fluid exuded, and one saw small granular areas, probably areas of bronchial pneumonia. Microscopically, only occasional areas of bronchial pneumonia were found.

The liver was enlarged, weighing 2,480 Gm. On the uncut surface, there were numerous raised granular areas about the size of a dime. On section of the organ, the granular portions stood out distinctly from the remainder of the liver tissue. Toward the center of the organ, these areas became confluent. The granular portion was much softer than the surrounding liver tissue, and could be removed by scraping with a knife. Many of the vessels in the upper portion of the right lobe were thrombosed. This was true of the portal veins and probably to some extent of the arteries.

Under the microscope, the liver cells in the granular necrotic areas were swollen and contained numerous small vacuoles, which with a sudan III stain revealed an increase in fat. Throughout the liver, the central veins were dilated, as were also the sinusoids about them. A moderate degree of chronic passive congestion of the organ was noted, with some destruction of the parenchymatous cells about the central vein. There was a marked increase in the peripheral connective tissue throughout the entire liver, and the periportal spaces were greatly widened with new formation of connective tissue. In some of these periportal areas in the right lobe, the hepatic artery and bile ducts appeared uninvolved in any process, but the portal vein could barely be recognized as such, because of the change that had taken place. The veins had a necrotic wall, and in many of them the lumen contained a small amount of fibrin and clot. In the tissue about the vessels, many lymphocytes and polymorphonuclear leukocytes were present. In some periportal areas, the veins were seen as thick-walled vessels with

connective tissue growing into the lumen. Many newly formed bile ducts were present in the periportal tissue, and an amitotic division of the cells was seen in the fibrous tissue in the periportal areas. Also in this area some of the branches of the hepatic arteries showed an acute and a subacute inflammatory change. The media of the affected vessels took a deep red stain and stood out as a hyaline mass. Some of the vessels which in places had disintegrated showed an infiltration of the hyaline layer with polymorphonuclear leukocytes. In the vessels undergoing this change, the media had completely or almost completely disappeared. The intima of the involved vessels showed a marked proliferative change. In many of the vessels in the acute state, the proliferation did not uniformly involve the whole wall, only a small irregular projection of fibrous tissue in the lumen being visible. In the late or granulomatous stage, the lumen was practically obliterated by a concentric ingrowth of the tissue. Lymphocytes were present in large numbers in the fibrous tissue in the external portion of the vessels. In the earlier stages of the disease, many of the vessels were thrombosed, and organization of the thrombus was taking place. About the thrombosed vessels and those showing the acute process were many polymorphonuclear leukocytes, chiefly located in the immediate vicinity of the necrotic hyaline wall or the thrombus, or about both. In a zone more distal to the lumen of the vessel were many lymphocytes and a few polymorphonuclear leukocytes.

About the vessels in which the lesion had passed into the subacute stage, lymphocytes alone were in the walls. Most of the involved vessels showed a concentric lesion. In a few of them, however, only one side was involved. Many of the arteries in the right lobe of the liver, measuring from 2 to 5 mm. in diameter, were involved in the process to a greater or lesser degree. The smaller branches of the hepatic artery, with a diameter of from 1 to 2 mm., were rarely involved. Although none was seen in the acute state, with the degenerative process in the wall, many were undergoing the process of endarteritis obliterans, and in the lumen of others there was a clot which was undergoing organization.

The wall of the gallbladder was thickened, the lumen was small, and on the mucosal surface were seen many fine white flakes of fibrin-like membrane. The cystic vein was thrombosed. Under the microscope, one saw that the wall of the gallbladder was thickened and infiltrated with many lymphocytes. The arteries of the organ had undergone a process of obliteration similar to that observed in the liver. The process was, however, in the more advanced stage. About the vessels there was a cellular fibrillar material with many lymphocytes. Around the intima were found a few broken, pink-staining fragments of the necrotic media containing lymphocytes and a few polymorphonuclear leukocytes. Over this necrotic media, there was a thickened intima which in many instances had nearly obliterated the lumen of the vessel. In some areas, the newly formed intima was covered with endothelium, and the lumen had become round and of more or less normal contour. In other vessels, no endothelium was noted on the surface, and the lumen was irregular, suggesting that the process had gone so far that only a small opening represented the lumen. Usually, these were noted on the outside of a concentric ring of fibrous tissue and were in all probability the vasa vasorum of the degenerated artery. In this organ again, the smaller vessels ranging to 0.2 mm. in size showed an endarteritic change, but did not show the granulomatosis periarteritica revealed by the large vessels. The cystic vein was thrombosed, and fibroblasts could be seen growing into the thrombus and organizing it. This vessel also showed a definite granulomatosis with thickened fibrous tissue wall and lymphocytes.

The spleen was enlarged and soft. On section, it presented the appearance of an acute splenic tumor. Microscopically, it showed a rather marked increase in fibrous tissue, especially about the blood vessels. The walls of the vessels were thickened by a clear hyaline connective tissue. No evidence of an acute arteritis was noted. Many large mononuclear leukocytes and eosinophils, as well as considerable blood pigment, were scattered diffusely throughout the organ. The malpighian corpuscles were about normal in size, but appeared to have decreased in number.

In the gross, the pancreas appeared normal, except for an occasional thrombosed artery. There was some increase in the fibrous tissue. Microscopically, a

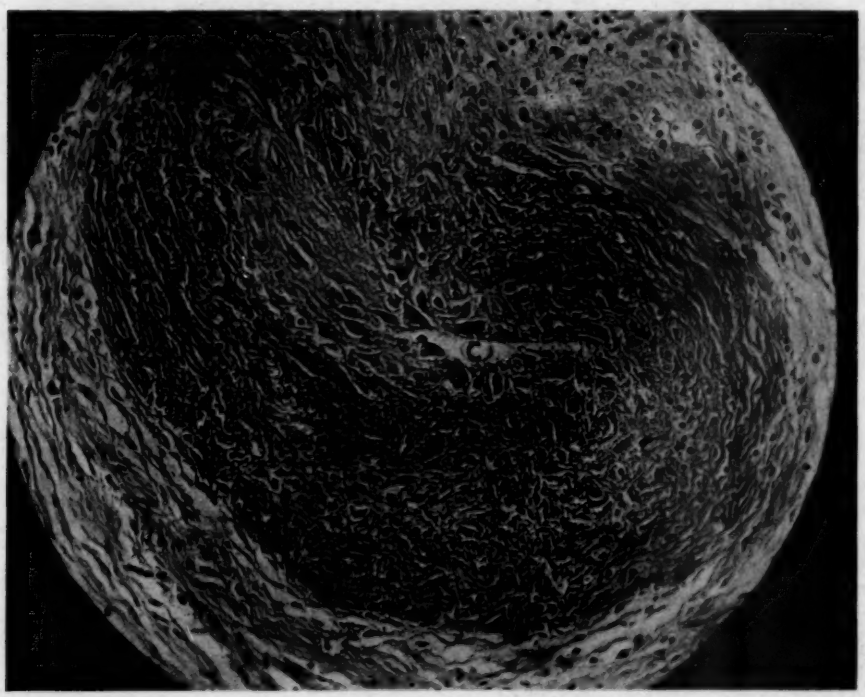

Fig. 1.—Cystic vein of gallbladder, which has been thrombosed and is nearly completely organized. *C* represents the remains of the lumen of the vessel.

considerable interlobular and intra-acinous fibrosis of the pancreas was present with much lymphocytic infiltration. The fibrosis was most apparent about the blood vessels, especially the arteries. The pancreatic cells in the immediate vicinity of the vessels were completely destroyed, while more distally the cells were swollen, large and granular. The island cells in the involved areas were degenerating, and only remnants of many cells were left. The arteries in the organ showed changes similar to those described in the liver. Here the process was in a relatively acute stage. In the small arteries, the endothelial cells were large, swollen and vacuolated, the intima of the vessels was thickened, and the arteries were undergoing an endarteritis obliterans. In the larger arteries with a lumen

from 2 to 5 mm. in diameter, the endothelium was completely absent, although many fibroblasts were present. In many of these vessels, thrombi were found in the lumen, but in other vessels, although no clot was seen, the granulomatosis was present and the wall of the vessel was more or less completely involved. Microscopically, many of the vessels were seen to be undergoing the same pathologic change that had been observed in other organs.

The kidneys were enlarged and together weighed 596 Gm. The capsule stripped readily, leaving a red, granular surface with small reddish areas the size of a pinhead. On section, the small red spots were seen to extend deep into the

Fig. 2.—Low power magnification of a branch of the right portal vein, showing a thrombus in the lumen; *A*, thrombus; *B*, organization of the thrombus; *C*, necrotic wall of the vein; *D*, fibrous tissue and compressed liver tissue.

kidney tissue, although they were much more prominent in the cortex. The glomeruli could be seen as small hemorrhagic points. The outer surface of the organs showed numerous shallow scars. Under the microscope, one noted a considerable increase in the interstitial tissue, and in some areas it took the form of large scars extending down from the cortex. In these areas, the kidney tissue was destroyed, and only a few small shrunken tubules and sclerosed glomeruli remained. A moderate degree of lymphocytic infiltration into the area was noted. In the remaining kidney substance, the greater number of glomeruli were enlarged,

and some of them had small plugs of fibrin at the base. These plugs lay in their afferent vessels about which the wall of the vessel had become necrotic. In other glomeruli, one or more capillary loops contained small plugs of fibrinous material occluding the lumen. The other involved capillary loops were small and shrunken and had fallen against the capsule of the glomerulus, where they appeared to have become adherent. Many of the capillaries containing emboli had ruptured with hemorrhage into the capsular cavity. In some glomeruli, the capillary lumen contained polymorphonuclear leukocytes in abundance. The endothelial cells in the glomeruli were swollen, and in places presented themselves as a mass in the capillary lumen. In areas, two or more of the desquamated epithelial cells had

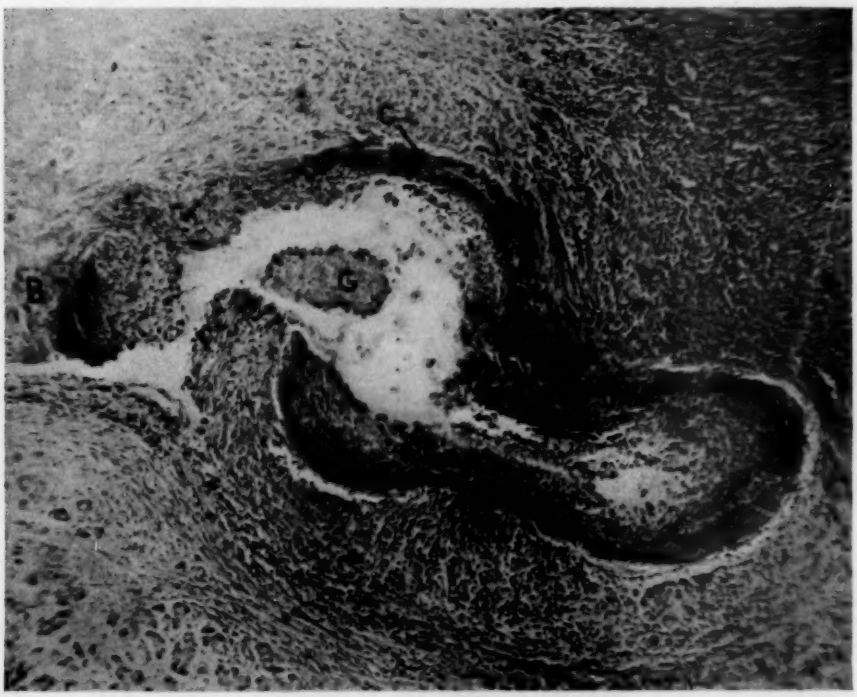

Fig. 3.—Section of artery in the pancreas showing acute degeneration of the arterial wall; *A*, pancreatic tissue; *B*, fibrous tissue about artery; *C*, necrotic media of vessel with ingrowth of fibrous tissue; *G*, thrombus.

fused together. In places, the capsular spaces were completely filled with red blood cells. In some areas, the tubules were small and presented a low cuboidal epithelium, while in the same field there were some large dilated tubules with necrotic material in the lumen. The lumen of many glomeruli was merely occluded by large, granular, swollen epithelial cells. Some of the cells in the epithelium of the tubules gave evidences of regeneration by the presence of from two to four nuclei. A marked lymphocytic infiltration was present in the interstitial tissue between the tubules and about the glomeruli. In the region of the involved arteries, many polymorphonuclear leukocytes were seen in and about the tubules.

The vessels of the kidney showed diffuse and rather acute involvement. Beginning with the arcuate vessels there was a periarteritic degeneration and proliferation and also a proliferation of the intima of the arteries. The lumen of many of the vessels was partially filled with a thrombus which in many cases had become organized. The endothelium had desquamated and could be seen as a clump of cells in the clot. The intima at points was proliferating and extending into the lumen of the vessels. It was composed of stellate cells resembling growing fibroblasts. The media of many of the vessels was necrotic, extending as a pink-staining ring of fibrin-like substance around the artery. There was a marked leukocytic reaction about the diseased arteries. Near the lumen of the vessel were many polymorphonuclear leukocytes. These were particularly numerous about the

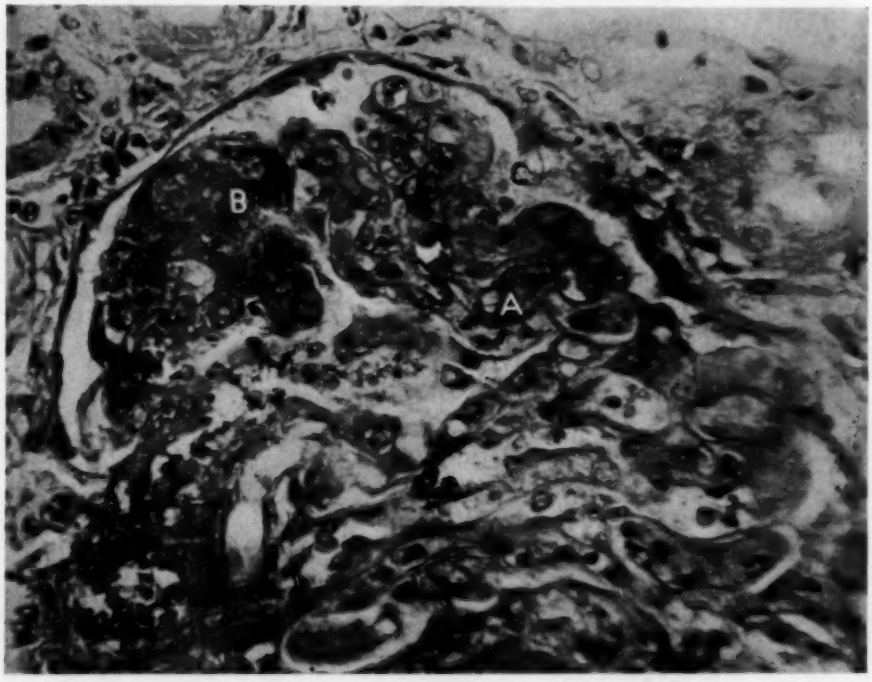

Fig. 4.—Section of the kidney showing: *A*, leukocytes in the dilated capillaries; *B*, necrotic glomerular loop; *C*, hemorrhage into the glomerular cavity.

necrotic media, and in areas appeared to have invaded the substance and caused its absorption. The adventitia was also greatly thickened, and fibrous tissue extended from it into the surrounding kidney tissue, producing large scars. Many lymphocytes were present in the scarred areas. The kidney tissue in the periphery of the involved arteries was destroyed, and the glomeruli had become small and hyalinized, the tubules contracted and the epithelium degenerated. Many lymphocytes were noted in the tubules in these areas. In other parts of the kidney, aside from the acute process, the picture was that of a lesion of chronic interstitial nephritis.

The stomach showed a typical hour-glass constriction with thickening near the pyloric end. On the mucosal surface, there was a shallow ulcer measuring from 0.5 to 1.5 mm. in diameter. About 3 cm. above the pylorus, at the point of constric-

tion of the stomach, a second ulcer, measuring 4.3 cm., was present on the lesser curvature. Its borders were ragged, but it had a clean base. A considerable thickening of the mucosa at the edge of the ulcer was noted. Under the microscope, the mucosa was seen to be eroded, and the base of both ulcers was clean. The duodenal ulcer extended also into the submucosa, while the one on the lesser curvature extended into the muscularis. At the base of the gastric ulcer, an artery showing an obliterative endarteritis was observed. In one section near the serous coat below the ulcer, a large artery was undergoing degeneration and inflammation of its wall.

The prostate was about two and a half times the normal size. On section, many nodules were found. Microscopically, a hypertrophy of the gland was noted.

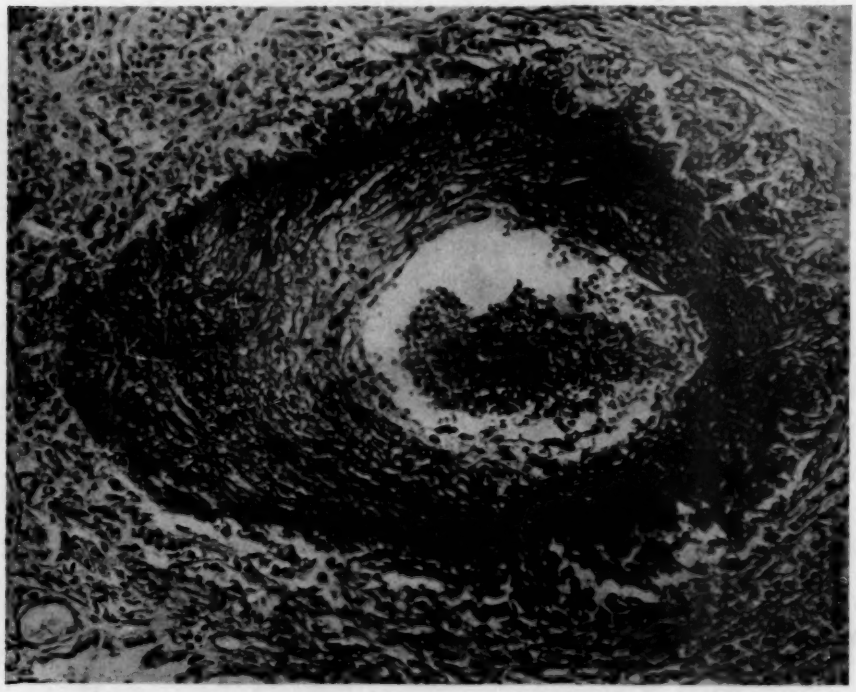

Fig. 5.—Arcuate artery of kidney showing degenerative and proliferative process in wall.

Some of the arteries showed changes similar to those noted in other organs. Here again the necrotic media, proliferation of the intima, infiltration of the vessel with polymorphonuclear leukocytes and thrombus in the vessel lumen were the prominent features.

The bladder was normal both grossly and microscopically. In the submucosa of the ileum under the endothelium of the vessels, irregular outlines of staining material which gave the staining reaction of fibrin were found. Around the material was a collection of leukocytes in which polymorphonuclears and lymphocytes played the most prominent part. There was here a marked proliferation of the intima with new fibroblasts. The lumen of the small capillaries was narrowed, and their walls were thickened by hyaline material.

In the gross, both suprarenal glands appeared normal. Microscopically, the vessels were congested, and there was a slight thickening of the intima, although no acute degeneration was present.

COMMENT

The correlation of the pathologic features with the clinical history of this case presents many points of interest. The essential lesion was a widespread periarteritis nodosa, with which the following clinical conditions were apparently connected: (1) jaundice, (2) hypertension and (3) changes in the peripheral nerves.

The widespread changes in the blood vessels of the liver and the gallbladder were presumably directly or indirectly responsible for the jaundice. There is justification for attributing the marked terminal hypertension to the changes in branches to the renal arteries, especially in the afferent glomerular vessels. These resembled closely the lesions described by Fahr [2] as a type of malignant hypertension. If the chief vascular lesions had been limited to the kidney, the picture would have corresponded to a moderately developed malignant hypertension in the sense of Fahr. Fahr suggested that periarteritis nodosa may be a cause of malignant hypertension. The clinical symptoms indicated disease of the peripheral nerves, a condition that has been associated with periarteritis nodosa in other cases. In our patient, because of the restriction imposed on the completion of the autopsy, it was not possible to study the peripheral nerves. Some doubt also exists concerning the relation of the vascular lesions to the gastric ulcer. A vessel at the base of the ulcer showed the typical vascular lesion found elsewhere. The clinical history indicated that the patient had suffered from gastric ulcer many years before, whereas the vascular lesions were certainly of more recent origin.

Of interest, also, is the relation of the periarteritic lesion to other pathologic changes in some of the organs. In the liver, pancreas and kidney, the focal increase and proliferation of connective tissue and the accumulation of lymphocytes, polymorphonuclear leukocytes, large monocytes and occasional plasma cells around vessels were apparently connected with the arterial lesions. The cirrhotic changes in the liver may have represented an extension of this process. In the heart, on the other hand, one found only a slight increase in connective tissue around the blood vessels, as might be expected from the absence of noticeable changes in the walls of the coronary vessels. In the spleen, there was an increase of connective tissue and later hyaline changes about the blood vessels. The enlargement of the prostate was independent of vascular changes.

2. Fahr, T., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 6.

In considering the character of the vascular lesions, one may distinguish between those found in vessels of medium size with a diameter of from 3 to 5 mm. and those in the smaller vessels. In the former, necrosis of the media was combined with infiltration by a hyaline material which behaved like fibrin and was associated with proliferation of the intima and in many cases with remarkable proliferation of the periarterial tissue. Here there was in places such a large accumulation of plasma cells and of large mononuclear cells as to suggest the term granulomatosis periarteritica. In the intima, the lining endothelium was often lost. The hyaline material reached into the lumen of the vessels and in places was taken up by phagocytes. In some areas showing injury to the endothelium and to the intima in general, thrombi developed and extended into the larger vessels. In later stages, when thrombi had become organized, their presence was indicated only by marked thickening of the intima. Connective tissue may also have partly or wholly organized the hyaline material with the media.

In the pancreas and the prostate, one noted hemorrhagic infiltration in the walls of certain blood vessels. This seems to have been due to an injury to the walls. Possibly similar were the lesions in the capsular space of the kidneys, where hemorrhage had occurred from the capillaries of the glomeruli in which afferent vessels had been occluded. In the smaller vessels, one found merely intimal proliferation or desquamation of vacuolated endothelial cells. In the afferent vessels of the glomeruli of the kidney frequent plaques of fibrin were seen. The glomerular capillaries were often occluded by endothelial cells. In the spleen, the smaller vessels showed only hyaline change, which seemed to have no relation to the general process. It is difficult to decide whether the difference between the smaller and the larger vessels is due to the fact that the former were less affected by the agent responsible for the disease, or whether it can be explained by a difference in structure of the two types of vessels. In different locations, however, the size of affected vessels varied considerably. The larger vessels, the aorta, for example, showed only the usual changes of arteriosclerosis, and these changes were especially marked in the abdominal portion near the origin of the larger branches. They apparently bore no relation to the specific lesion of periarteritis nodosa.

The organic distribution of the lesions is of great interest. It is quite apparent that abdominal organs were mainly affected. The lungs were free from the disease, and the heart showed only a small amount of lymphocytic infiltration about some of the coronary vessels. In the organs of the abdomen, with the exception of the liver and the gallbladder, the arteries and arterioles were alone primarily involved. In

the gallbladder, the arteries and the veins showed extensive lesions, and the cystic vein was completely thrombosed. The thrombosis of the cystic veins is significant in connection with the location of the hepatic lesion in the dome of the right lobe. The cystic vein drains into the right branch of the portal vein, which is distributed to the right lobe of the liver. The localization in the dome of the organ may have been due to the "stream line" effect of the portal blood, as has been pointed out by Copher and Dick.[3] From the pathologic point of view, the oldest and most extensive lesions were found in the gallbladder, and it is suggested that the process started there and that the agent was borne by the blood to the other organs. The fact that the lungs were uninvolved might be explained on the basis of a patent foramen ovale. Perhaps the agent, at first generally distributed in the form of a toxin, manifested itself as a peripheral neuritis, and later became localized in the biliary tract.

SUMMARY

A detailed examination of a case of periarteritis nodosa revealed the usual pathologic changes described in the literature. The lesions were most prominent in vessels of the abdominal organs, an observation which has been reported in a number of other cases.[4]

In addition, the oldest and most extensive lesions were found in the gallbladder, where both arteries and veins were affected. The portal veins in the dome of the right lobe of the liver were extensively involved. That area in the liver represents the area of drainage from the gallbladder. It is suggested that perhaps the primary lesion was in the gallbladder and that the agent was borne by the blood to the other tissues of the body.

3. Copher, G. H., and Dick, B. M.: "Stream Line" Phenomena in Portal Vein and Selective Distribution of Portal Blood in Liver, Arch. Surg. **17**:408 (Sept.) 1928.

4. Weilder, V.: Ztschr. f. Path. **25**:305, 1923.

INFARCTS OF THE LIVER AND THE MECHANISM OF THEIR PRODUCTION

REPORT OF A CASE *

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Infarcts of the liver, if the term is used in the restricted sense in which it is customarily used for other organs of the body, namely, to signify necrosis of a part resultant from the shutting off of the blood supply to that part, are of infrequent occurrence. This fact has led observers from time to time to include conditions affecting the liver other than infarcts but superficially resembling them, so that at present a wide variety of dissimilar anatomic pictures are described in the literature under the all-inclusive term of infarcts of the liver. These pseudo-infarcts will be enumerated and discussed briefly. There are, of course, reports of cases of true infarct of the liver in the literature, and those that were accessible have been summarized and tabulated chronologically.

Only in recent years has attention been called to the combination of factors that must be operative in order that true infarcts of the liver may result. Nowhere, however, are these factors brought together in one place and evaluated. A lack of appreciation of all the factors involved led the early workers in the experimental production of this type of lesion to erroneous conclusions, and it accounts also for the confusion that exists in the literature on the subject. Brief mention will be made of some of the results in the experimental production of this type of damage of the liver, and with these results as a background, the mechanism of infarction of the liver will be outlined. Finally, a case of infarct of the liver occurring in a child aged 31 hours will be reported in some detail.

OBSERVATIONS RECORDED IN THE LITERATURE

Effects of Occlusion of the Portal Vein.—That occlusion of large branches of the portal vein, and even occlusion of the main stem of this vessel, will not produce infarcts in the liver is adequately proved by the numerous case reports of this condition as well as by the experimental

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* From the Department of Pathology, Yale University School of Medicine.

evidence. Borrmann,[1] Botkin,[2] Heller,[3] Paulicki,[4] Pick,[5] Rolleston,[6] Saxer,[7] Versé [8] and Wagner [9] all cited examples of thrombosis of the portal vein without resultant infarcts or necrosis of the liver; nearly all, however, called attention to the decreased size of the liver in this condition about which more will be said. There are many more examples in the literature of occlusion of the portal vein in which no other effect than the diminution in the size of the liver is mentioned. The statement is now generally accepted that in a gradual exclusion of the venous supply to the liver the hepatic artery is capable of assuming the required venous function. This was believed by Cohnheim and Litten [10] and also by Woolridge,[11] and has since often been quoted as a fact. Experimental occlusion of this vein, even when more or less instantaneous, by Rous and Larimore,[12] by Lewis and Rosenow,[13] and even by Cohnheim and Litten, failed to produce infarcts. In the report of a case of obliteration of the portal vein, Osler [14] stated the reason for the failure of infarction to take place as follows: After complete exclusion of portal blood from the organ, the lobular capillary plexus continues filled, as the venules which collect the blood from the

1. Borrmann: Beiträge zur Thrombose des Pfortaderstammes, Deutsches Arch. f. klin. Med. **59**:283, 1897.

2. Botkin: Krankheitsgeschichte eines Falles einer Pfortaderthrombose, Virchows Arch. f. path. Anat. **30**: 449, 1864.

3. Heller, A.: Ueber traumatische Pfortaderthrombose, Verhandl. d. deutsch. path. Gesellsch. **7**:182, 1904.

4. Paulicki: Thrombose des Pfortaderstammes, bedingt durch in die Pfortaderverzweigungen hineinwuchernde Krebsmassen, Berl. klin. Wchnschr. **4**:505, 1867.

5. Pick, L.: Ueber totale hämangiomatöse Obliteration des Pfortaderstammes und über hepatopetale Kollateralbahnen, Virchows Arch. f. path. Anat. **197**:490, 1909.

6. Rolleston, H. D.: Liver in Hepatic and Portal Thrombosis, Tr. Path. Soc. London **50**:148, 1898-1899.

7. Saxer, F.: Beiträge zur Pathologie des Pfortaderkreislaufs, Centralbl. f. allg. Path. u. path. Anat. **13**:577, 1902.

8. Versé, M.: Ueber die cavernöse Umwandlung des periportalen Gewebes bei alter Pfortaderthrombose, Beitr. z. path. Anat. u. z. allg. Path. **48**:526, 1910.

9. Wagner, E.: Beiträge zur Pathologie und pathologischen Anatomie der Leber, Deutsches Arch. f. klin. Med. **34**:520, 1884.

10. Cohnheim, J., and Litten, M.: Ueber Circulations-Störungen in der Leber, Virchows Arch. f. path. Anat. **67**:153, 1876.

11. Woolridge, L. C.: On Hemorrhagic Infarction of the Liver, Tr. Path. Soc. London **39**:421, 1888.

12. Rous, P., and Larimore, L. D.: Relation of the Portal Blood to Liver Maintenance, J. Exper. Med. **31**:609, 1920.

13. Lewis, D. D., and Rosenow, E. C.: Primary Portal Thrombosis, Arch. Int. Med. **3**:232 (April) 1909.

14. Osler, W.: Case of Obliteration of the Portal Vein, J. Anat. & Physiol. **16**:208, 1882.

capillaries of the hepatic artery empty directly into the portal interlobular vessels, and the blood supply is in this way maintained.

Occlusion of the Interlobular Venules.—From the observations mentioned it is apparent that any block to the interlobular portal vessels will result in a focal area of infarction. As early as 1869, Klebs [15] attributed infarcts in the liver to this cause. On this basis did Schmorl [16] account for the liver changes in puerperal eclampsia. In mentioning Schmorl's observations Chiari [17] called attention to the occurrence of similar focal zones of necrosis in the liver in man following occlusion by emboli of interlobular branches of the portal vein. Mallory [18] considered the focal zones of necrosis occasionally seen in the livers of guinea-pigs as miliary infarctions due, in one class of cases, to cell emboli brought from the spleen to the liver by the portal vein and lodged in the minute branches of the portal vein. Osler [19] attributed hemorrhagic infarcts in the liver in a case he reported in 1887 to thrombi in the interlobular venules, associated with obliteration of branches of the hepatic artery by an increase in the interlobular connective tissue. Similarly, Steinhaus [20] reported a case of infarction of the liver due to complete occlusion of the interlobular branches of the portal vein by fibrosis following an endophlebitis, and Winternitz [21] mentioned softened hemorhagic infarcts in the liver resulting from "thrombosis of minute portal vessels."

Occlusion of the Hepatic Artery.—The matter of changes in the liver produced by interference with the arterial supply is in a much more confused state. The experiments of Cohnheim and Litten [10] on the ligation of the hepatic artery in rabbits at a point beyond the origin of the right gastric artery showed that infarcts of the liver were an invariable result. These experiments were repeated by Janson [22] on rabbits with like results, but when performed on dogs no liver changes

15. Klebs, E.: Handb. d. path. Anat. **1**:454, 1869.

16. Schmorl: Pathologisch-anatomische Untersuchungen über Puerperaleklampsie, Leipzig, 1893.

17. Chiari: Erfahrungen über Leberinfarcte, Centralbl. f. allg. Path. **9**:839, 1898.

18. Mallory, F. B.: Necroses of the Liver, J. M. Research **6**:264, 1901.

19. Osler, W.: Notes on Hemorrhagic Infarction, Tr. A. Am. Phys. **2**:133, 1887.

20. Steinhaus, F.: Ein seltener Fall von Pfortaderthrombose mit hämorrhagischer Infarzierung und Nekrotisierung der Leber, Deutsches Arch. f. klin. Med. **80**:364, 1904.

21. Winternitz, M. C.: The Effect of Occlusion of Various Hepatic Vessels upon the Liver, Bull. Johns Hopkins Hosp. **22**:395, 1911.

22. Janson, C.: Ueber Leberveränderungen nach Unterbindung der Arteria hepatica, Beitr. z. path. Anat. u. z. allg. Path. **17**:505, 1895.

were observed. His results in rabbits were confirmed by Behrend,[23] and Whipple and Sperry [24] in their experiments on chloroform poisoning confirmed his observations in dogs. De Dominicis [25] in 1891, four years before the report of Janson's work, obtained the same results in dogs. Behrend, Radasch and Kershner [26] summarized the effects of ligation of the hepatic artery on the livers of different animals in this manner: Rabbits and guinea-pigs always succumb to successful peripheral ligation. Dogs and cats resist the ligation and continue to live indefinitely in spite of a combination of a peripheral and central ligation.

A rather fanciful explanation for the failure to produce infarcts in dogs was supplied by Stolnikow,[27] who failed to find damage of the liver following the simultaneous ligation of the portal vein and the hepatic artery and attributed that result to an adequate blood supply to the liver by way of a reverse current in the hepatic veins. In this connection, it is interesting to note the work of Chandler,[28] who ligated temporarily the hepatic artery and the portal vein in Eck fistula dogs for periods as long as twelve hours and failed to find necrosis of the hepatic parenchyma. He attributed his results purely to the power of the hepatic cells to resist local anemia.

De Dominicis believed that ligation of the hepatic artery in dogs failed to produce hepatic infarcts because the blood supply by way of the portal vein was adequate for nutrition. The belief in the adequacy of either part of the double hepatic circulation for liver maintenance is widespread, and the double circulation is the often quoted reason for the infrequent occurrence of infarcts of the liver. That another explanation is more probably the correct one for this observation is obvious from what follows.

Doyon and Dufourt [29] were the first to maintain that the reason infarct did not occur in the liver in dogs following ligation of the hepatic artery was because the liver received an adequate arterial blood supply

23. Behrend, M.: Experimental Ligation of Hepatic Artery, Surg. Gynec. Obst. **31**:182, 1920.

24. Whipple, G. H., and Sperry, J. A.: Chloroform Poisoning. Liver Necrosis and Repair, Bull. Johns Hopkins Hosp. **20**:278, 1909.

25. De Dominicis, N.: Observations expérimentales sur la ligature de l'artérie hépatique, Arch. ital. de biol. **16**:28, 1891.

26. Behrend, M.; Radasch, H. E., and Kershner, A. G.: Comparative Results of the Ligation of the Hepatic Artery in Animals, Arch. Surg. **4**:661 (May) 1922.

27. Stolnikow: Die Stelle vv. hepaticarum im Leber- und gesammter Kreislaufe, Arch. f. d. ges. Physiol. **28**:255, 1882.

28. Chandler, L. R.: Resistance of Hepatic Tissues to Local Anemia, Proc. Soc. Exper. Biol. & Med. **18**:23, 1920-1921.

29. Doyon and Dufourt: Contribution à l'étude de la fonction uréopoiétique du foie, Arch. de physiol. norm. et path. **10**:522, 1898.

from the other branches of the celiac axis. In 1905, Haberer [30] explained more fully such observations by pointing out that ligation of the main stem of the hepatic artery central to the origin of the right gastric artery produces no effect on the liver because of the collateral circulation through this right gastric. Ligation of the hepatic artery peripheral to the right gastric also fails to produce hepatic infarcts because the gastroduodenal artery immediately establishes a collateral circulation. Ligation of the hepatic artery just before it divides into the right and left branches produces infarcts, he stated, in many dogs and cats. In the animals in which this procedure is without effect, the explanation can be found in the fact that in these animals each lobe of the liver receives an artery, any one of which may arise from the main stem of the hepatic artery and may thus escape being caught in the ligature. Segall [31] correctly attributed failure of infarcts to take place following ligation of the hepatic artery to an anastomosis between the branches of the hepatic artery and the phrenic vessels, which forms a communication between the thoracic and the abdominal circulations. He was led to conclude that "infarcts of the liver follow obliteration of those arteries which terminate in the liver without sending any branches to the subcapsular system of anastomoses, and which are therefore proper end-arteries." Other vessels cited by von Hofmeister [32] as being capable of establishing an arterial collateral circulation to the liver are those present in adhesions between the hepatic capsule and adjacent abdominal organs, and also an artery in the ligamentum teres. To this list may be added anomalous arteries to different lobes of the liver. In all essential details, the hepatic arterial circulations of dogs and man are identical (fig. 1).

Examples of Occlusion of the Hepatic Artery in Man without Resultant Infarcts of the Liver.—In 1903, Kehr [33] reported the first case of a successful ligation of the arteria hepatica propria in a patient who had an aneurysm of the right branch of the hepatic artery that had perforated into the gallbladder. This patient survived and showed no evidence of damage of the liver. In 1920, Smith [34] reported a deliberate

30. Haberer, H.: Experimentelle Unterbindung der Leberarterie, Arch. f. klin. Chir. **78**:557, 1905.

31. Segall, H. N.: An Experimental Anatomical Investigation of the Blood and Bile Channels of the Liver, Surg. Gynec. Obst. **37**:152, 1923.

32. Von Hofmeister, F.: Unterbindung der Arteria hepatica propria ohne Leberschädigung, Zentral. f. Chir. **49**:154, 1922.

33. Kehr, H.: Der erste Fall von erfolgreicher Unterbindung der Arteria hepatica propria wegen Aneurysma, München. med. Wchnschr. **50**:1861, 1903.

34. Smith, R. E.: Ligature of the Hepatic Artery, Brit. J. Surg. **8**:532, 1920-1921.

ligation of the hepatic artery with no ill effects in a person in whom this vessel was injured in the course of a gallbladder operation. Von Hofmeister [32] reported a similar successful ligation of the hepatic artery distal to the origin of the right gastric artery in a case in which the gastroduodenal artery was also ligated in the course of an extensive gastric resection. In detailing the finding of a thrombosed aneurysm of the hepatic artery at autopsy, Tuffier [35] stressed the slowness of the occlusion as the factor responsible for the lack of damage to the liver. Merkel [36]

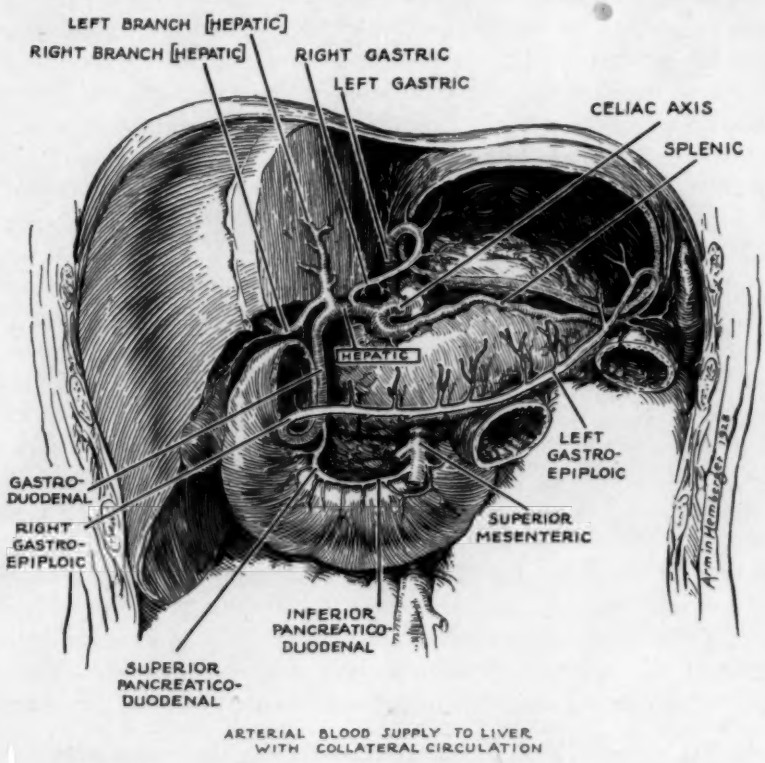

Fig. 1.—A drawing showing the arterial blood supply of the liver with the collateral circulation.

described a thrombosed aneurysm of the arteria hepatica propria central to the origin of the right gastric artery found accidentally at autopsy in a man 56 years of age who died of postoperative peritonitis. He attributed the lack of changes in the liver in this case to an adequate collateral circulation through the right gastric and the gastroduodenal

35. Tuffier, T.: Anéurisme de l'artère hépatique, Presse méd. **17**:153, 1909.

36. Merkel, H.: Zur Kenntnis der Aneurysmen im Bereich der Arteria hepatica, Virchows Arch. f. path. Anat. **214**:289, 1913.

arteries, and he also stated as his belief that this collateral circulation was aided by the slow formation of the thrombus in the aneurysm.

Examples of Pseudo-Infarcts.—In 1895, Pitt [37] reported an infarct of the liver in a man, aged 36, who died following an injury to his abdominal wall. "A branch of the portal vein to the right lobe of the liver was found to contain a recent thrombus . . . . . and an infarction had resulted." Four years later, Lazarus-Barlow [38] reported a similar case in a man 25 years of age who was crushed between buffers while pursuing his occupation of railway shunter. In the center of a pale yellow mass of tissue 2 inches (5 cm.) in length and nearly 1½ inches (3.7 cm.) in greatest width were "certain branches of the portal vein obstructed by thrombus. It is an indubitable anemic infarct." Heile [39] and Orth [40] both described "traumatische anämisch-necrotische Infarkte" of the liver and attributed their production to tears in branches of both the portal vein and the hepatic artery. Numerous other examples of infarcts of the liver following trauma are described which will not be enumerated here. It is without question, however, an erroneous concept to attribute these infarcts to occlusion of branches of the portal vein. The possibility always exists that the necrosis of the liver cells is the direct result of trauma and that the thrombi in the portal radicles are the result of, or are simultaneous with, this necrosis and not its cause.

Mention has already been made of the atrophy that results in the liver following occlusion of the portal vein. In discussing this atrophy in 1898, Zahn [41] called attention to the similarity in the gross appearance between this condition of the liver and the condition of "red infarcts" in the lung. He stated precisely that in the liver it is atrophy and not true necrosis, and he termed it "atrophic red infarcts of the liver" (atrophische rote Leberinfarkte) only because it resembled the condition of true infarcts of the lung. That same year, Chiari [42] reported seventeen cases of "genauer untersuchte Fälle von atrophischen

37. Pitt, G. N.: Cases of Portal Thrombosis with and without Infarction of the Liver, Tr. Path. Soc. London **46**:74, 1895.

38. Lazarus-Barlow, W. S.: A Case of Anemic Infarct in the Liver, Brit. M. J. **2**:1342, 1899.

39. Heile: Ueber einen traumatischen, anämisch-nekrotischen Leberinfarkt mit ausgedehnten Regenerationserscheinungen, Beitr. z. path. Anat. u. z. allg. Path. **28**:443, 1900.

40. Orth, J.: Ueber traumatische anämisch-necrotische Infarcte der Leber, Verhandl. d. deutsch. path. Gesellsch. **3-4**:82, 1900-1901.

41. Zahn, F. W.: Ueber die Folgen des Verschlusses der Lungenarterien und Pfortaderäste durch Embolie, Verhandl. Gesellsch. deutsch. Naturforsch. u. Arzte **2**:9, 1898.

42. Chiari: Erfahrungen über Infarctbildungen in der Leber des Menschen, Verhandl. d. deutsch. path. Gesellsch. **1-2**:13, 1898-1899.

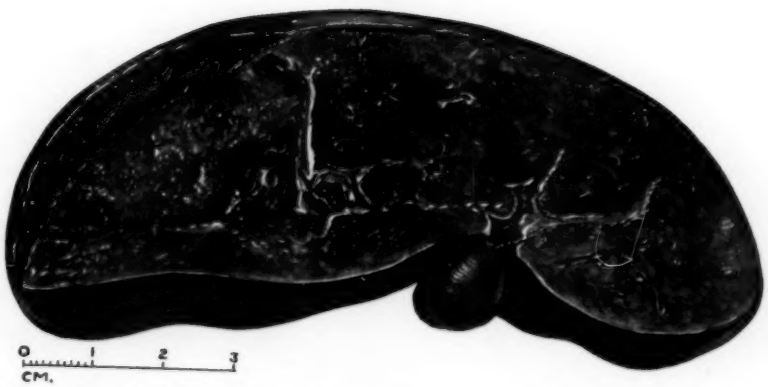

Fig. 2.—Hypoplasia of hepatic artery; embolus in portal vein; infarct of liver.

roten Infarkten," and somehow the impression was further extended by other reports of similar cases bearing the misleading term of atrophic red infarcts.

Occlusion of the Hepatic Veins.—Longcope,[43] Sternberg[44] and Versé[45] reported cases of thrombosis of the hepatic veins with necrosis of adjacent liver tissue as examples of infarcts of the liver. That necrosis of the liver is associated with thrombosis of the hepatic vein is proved without question by the case reports of these and of numerous other writers, but if we conform to our definition that an infarct is necrosis produced by an interference with the blood supply to a part, then these examples of interference with the blood supply from the liver fall outside the realm of our discussion.

In the accompanying table are listed in chronologic order all the available reports of cases of true infarct of the liver in the literature.

REPORT OF CASE

History.—The patient was the product of the fifteenth pregnancy, which was complicated by a dry labor lasting four days and resulting in a breech delivery. Premature rupture of the membranes occurred in the morning of Dec. 24, 1927, and the pains which set in shortly afterward were not severe until the evening of December 27. At this time, a physician was called for the first time. He found the fetus in the right sacro-anterior position, the anterior foot presenting and protruding through the cervix. An unsuccessful attempt was made to dilate the cervix with a Voorhees' bag, and so manual dilatation of the cervix was performed, at 9 a. m. the following day. Meconium was being passed at the time of the pains. The child was delivered with forceps on the after-coming head, because pressure could not be applied through the mother's abdomen, which was unyieldingly rigid. Following delivery, the baby failed to make any attempt at respiration; hence tubbing and mild stimulation were resorted to, the child breathing normally after an hour and a quarter of this treatment.

On examination, the infant was found to be entirely inert. Spanking produced arching of the back and turning of the head to the right, with movement of the right arm. In the course of the day, the infant became cyanotic and the respirations feeble. During the night it had several convulsions, during which the head was retracted and the arms and legs became rigid. Spinal fluid showed definite xanthochromia. There was a marked positive Chvostek sign, with left facial weakness. The abdomen was full, and the abdominal reflexes could not be obtained. All the other reflexes were hyperactive. The upper as well as the lower extremities were spastic. When the baby was touched, convulsive twitchings were induced. The Kernig sign was strongly positive, as was also the Babinski sign on both sides. Tapping the tendons of the knee induced spastic flexion of the legs and tension of the muscles to such a degree that the knee

43. Longcope, W. T.: Hepatic Infarctions, Pennsylvania Univ. Med. Bull. **14**:223, 1901-1902.

44. Sternberg, C.: Ueber obliteration der Vena cava inferior und Thrombose der Venae hepaticae, Verhandl. d. deutsch. path. Gesellsch. **10**:131, 1906.

45. Versé, M.: Ueber totale Pfortaderobliteration und anämische Infarkte der Leber, Verhandl. d. deutsch. path. Gesellsch. **13**:314, 1909.

Chronologic List of Reports of True Infarct of the Liver

Case	Year	Reported by	Condition in Liver	Mechanism of Infarction	Remarks
1	1877	Ross, G., and Osler, W.: Aneurysm of Hepatic Artery, Canada J. Med. & Surg. **6**: 1, 1877	"Numerous areas of necrosis which subsequently became, by inflammation and a sequestrating suppuration, converted into abscesses"	Laminated thrombus in aneurysm at bifurcation of hepatic artery, but occupying chiefly the right branch	.....
2	1887	Osler [19]	Hemorrhagic infarction	"Interlobular connective tissue growth obliterated a majority of the hepatic artery branches in the affected region, and had thus converted certain trunks of the venae portae into terminal vessels which, when plugged with solid thrombi, induced a condition of infarction in the area supplied by them"	.....
3	1891	Köhler, B.: Ueber die Veränderungen der Leber infolge des Verschlusses von Pfortaderasten, Inaug.-Diss., Göttingen, 1891	Zone of necrosis and multiple abscesses	Ulcerative endocarditis and embolus in branch of hepatic artery	Multiple abscesses in spleen and kidneys also; question of whether the infection or the thrombus was first in liver
4	1895	Ogle, C.: Infarcts in the Liver, Tr. Path. Soc. London **46**: 73, 1895	Infarcts from pea to hazel-nut size	"The hepatic artery is blocked at its bifurcation by adherent brick-colored clot"	Infarcts also in spleen and kidneys
5	1898	Chiari: Erfahrungen über Infaretbildungen in der Leber des Menschen, Ztschr. f. Heilk. **19**: 475, 1898	Multiple anemic infarcts	Ligature thrombus in gastric veins following pyloric resection, with emboli in interlobular branches of portal vein	.....
6	1898	Chiari (See reference for case 5)	Multiple anemic infarcts	Thrombi in veins of large intestine in a case of dysenteria follicularis, with emboli in interlobular branches of portal vein	.....
7	1898	Chiari (See reference for case 5)	Complete necrosis	Mitral endocarditis; embolus in arteria hepatica propria beyond the origin of the right gastric artery	.....
8	1898	Chiari (See reference for case 5)	Multiple hemorrhagic and necrotic infarcts	Endocarditis with emboli in smaller branches of hepatic artery	.....
9	1899	Castaigne, J.: Infaretus hemorrhagique très étendu du foie, Bull. Soc. anat. d Paris **1**: 150, 1899	Hemorrhagic infaret	Apical cardiac aneurysm; cardiac thrombus; multiple emboli	Emboli also to spleen, kidneys and lungs
10	1902	Baldwin, F. A.: Multiple Anemic Infarets of the Liver, J. M. Research **8**: 431, 1902	Multiple anemic infarcts	Aortic stenosis; cardiac dilatation; thrombus in right auricle	Infarcts also in brain, lungs, spleen, kidneys, stomach and duodenum
11	1904	Steinhaus [20]	Extensive necrosis and true hemorrhagic infarcts	Complete occlusion of interlobular branches of portal vein by fibrosis following endophlebitis	.....
12	1905	Ruczynski, B.: Zur kenntnis der arteriellen Infaretbildungen in der Leber des Menschen, Ztschr. f. Heilk. **26**: 147, 1905	Multiple zones of necrosis	Emboli and thrombi in hepatic artery	The corresponding portal vein branches and hepatic veins were thrombosed "secondarily to the embolism of the hepatic artery"
13	1909	Versé [45]	Widespread early ischemic infaret	Ligation of common hepatic artery and resection of left branch in course of operation for gastric carcinoma	.....

Chronologic List of Reports of True Infarct of the Liver.—Continued

Case	Year	Reported by	Condition in Liver	Mechanism of Infarction	Remarks
14	1911	Winternitz [21]	Softened hemorrhagic infarcts	Thrombosis of minute portal vessels	Primary carcinoma of stomach, with secondary invasion of liver
15	1916	Narath, A.: Ueber Entstehung der anämischen Leber nekrose nach Unterbindung der Arteria hepatica und ihre Verhütung durch arterio-portale Anastomose, Deutsche Ztschr. f. Chir. **135**: 306, 1916	Multiple abscesses and dry yellow necrosis	Ligature on hepatic artery between right gastric and gastroduodenal artery	Death in twenty days
16	1916	Narath (See reference for case 15)	Necrosis of right lobe	Aneurysm of right branch of hepatic artery with ligation	Patient recovered; recovery attributed to the fact that the formation of the aneurysm provided sufficient time for establishment of collateral circulation
17	1916	Narath (See reference for case 15)	Large necrotic shreds of liver with rupture through abdominal incision of an old necrotic zone of softening of the liver	Ligation of hepatic artery in course of a cholecystectomy	Patient recovered; possibly because of adequate collateral circulation from the numerous adhesions between superior surface of liver and anterior abdominal wall
18	1916	Narath (See reference for case 15)	Complete necrosis	Ligation of hepatic artery in course of operation for gastric carcinoma	.....
19	1916	Narath (See reference for case 15)	Complete necrosis of left lobe	Ligation of left branch of hepatic artery in course of operation for gastric ulcer	Death in seven days
20	1916	Narath (See reference for case 15)	Widespread necrosis of left lobe	Ligation of left branch of hepatic artery in course of operation for gastric carcinoma	Death in seventeen days
21	1916	Narath (See reference for case 15)	"Signs of liver necrosis" in right lobe	Ligation of right branch of hepatic artery in cholecystectomy	Patient recovered after "months" of illness
22	1916	Narath (See reference for case 15)	Complete necrosis of left lobe	Ligation of left branch of hepatic artery in course of operation for hydatid cyst in lobus quadratus	Death in four days
23	1916	Narath* (See reference for case 15)	Complete necrosis of right lobe	Ligation of right branch of hepatic artery in course of removal of a "tumor" in right lobe of liver	Death in seventy-two hours
24	1924	Mittasch, G.: Beiträge zur pathologie der Leber, Virchows Arch. f. path. Anat. **251**: 688, 1924	Multiple red infarcts	Organization of emboli and obliterating endarteritis in hepatic arteries	Infarcts also in kidneys; passive congestion of liver
25	1925	Cain, A., and Baltanski: Nécrose hémorrhagique du foie, Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 1450, 1925	Hemorrhagic necrosis	Not stated	Occurred in the course of a tuberculous bronchopneumonia
26 and 27	....	Rattone and Mondino (quoted by Raczynski)	Hemorrhagic infarcts in both cases	Simultaneous occlusion of portal vein (thrombosis) and hepatic artery (cirrhosis)	.....

* All nine cases cited by Narath were taken by him from the literature without mention of source. The 16th, 17th and 21st cases cited by him are questionable examples of true infarcts, since in each instance the patient recovered and the liver was not examined microscopically.

jerks could not be obtained. Ankle clonus was moderately sustained on both sides. There was a large extravasation of blood in the left fundus oculi. The baby died thirty-one hours after she was born.

Necropsy.—The examination was performed sixteen hours post mortem. The positive observations were limited to the heart, liver, left suprarenal gland and cranial contents, and these are described in order.

In the heart a widely patent ductus arteriosus joined the pulmonary artery to the aorta, and this ductus had the same diameter as the aorta which it joined. Numerous red, flame-shaped subepicardial hemorrhages were present on the anterior surface. A large interauricular septal defect converted the two auricles into a single cavity. A delicate velamentous strand of connective tissue at the inferior margin of the interauricular septal defect represented all that was present of the interauricular septum. The foramen ovale was patent. The muscular interventricular septum was intact. The thickness of the right ventricular wall was equal to that of the left, but the right cavity was only about half the size of the left.

The right lobe of the liver projected 3 cm. below the costal margin in the midclavicular line; the left lobe was not visible below the costal margin. Beneath the capsule of the left lobe on the diaphragmatic surface was a boggy mass of semisolid blood. This subcapsular extravasation involved the whole superior surface of the left lobe and had a sharply defined margin. Blood-tinged fluid exuded from the capsule overlying this hemorrhage and oozed into the peritoneal cavity. The inferior vena cava, the umbilical vein, the mesenteric vessels, the portal vein and the hepatic artery were all free from blood clots. The prominent umbilical vein entered the liver at the porta hepatis, and its connection with the ductus venosus and with the portal vein was readily traced. Section of the liver (fig. 2) revealed a left lobe which was completely infarcted and which had a soft yellow opaque center. The periphery of this central necrotic zone was composed of a deep red margin of varying thickness and of irregular outline which shaded off on the right with the normal parenchyma of that lobe of the liver. It was a portion of this hemorrhagic periphery that immediately underlay the subcapsular hemorrhage. Examination of the blood vessels supplying the liver brought to view a number of interesting conditions. The hepatic artery was markedly hypoplastic and had an unusually narrow lumen. Where it bifurcated into the right and left branches, the lumen became of pinpoint size. At the entrance of the portal vein into the liver was a firm, friable antemortem blood clot which completely blocked its lumen and extended farther into the umbilical vein and into the ductus venosus, shutting off their lumina also. These three vessels were lined by pale intima, and none showed any gross evidence of infection.

Microscopically, a large number of well preserved red blood cells were seen lying beneath that portion of the liver capsule which overlay the infarct. The adjacent liver cells (fig. 3) no longer formed definite columns. Their cytoplasm was granular and vacuolated; the nuclei were fragmented and pyknotic, in many instances lying extruded outside their cells. The spaces between these cells were wide and irregular and markedly engorged with blood. In areas far removed from the liver capsule, the picture was somewhat different. Here the lobular structure was more or less intact, but the liver cells were of irregular outline, pale and devoid of nuclei. The liver sinusoids were widely dilated, and were empty in some places and filled with laked red blood cells in others. In areas in which the lobules were sufficiently preserved to make a study of their structure possible, the central veins were found intact and unobstructed. The branches of the hepatic arteries lying in the periportal spaces had greatly narrowed lumina,

and as a consequence their walls appeared thickened. Leukocytic cellular infiltrations, composed in the main of polymorphonuclear leukocytes with unusually large numbers of eosinophils, were present in the periportal areas surrounding the ramifications of the portal vein. The periportal or interlobular venules were free from thrombi or emboli.

The left suprarenal gland weighed 10 Gm., which was three times the weight of the right suprarenal gland. An extensive hemorrhage was present in both the cortex and the medulla. Microscopic examination showed the cortical cells to be well preserved, though separated by hemorrhage. In the medulla, many suprarenal cells were necrotic.

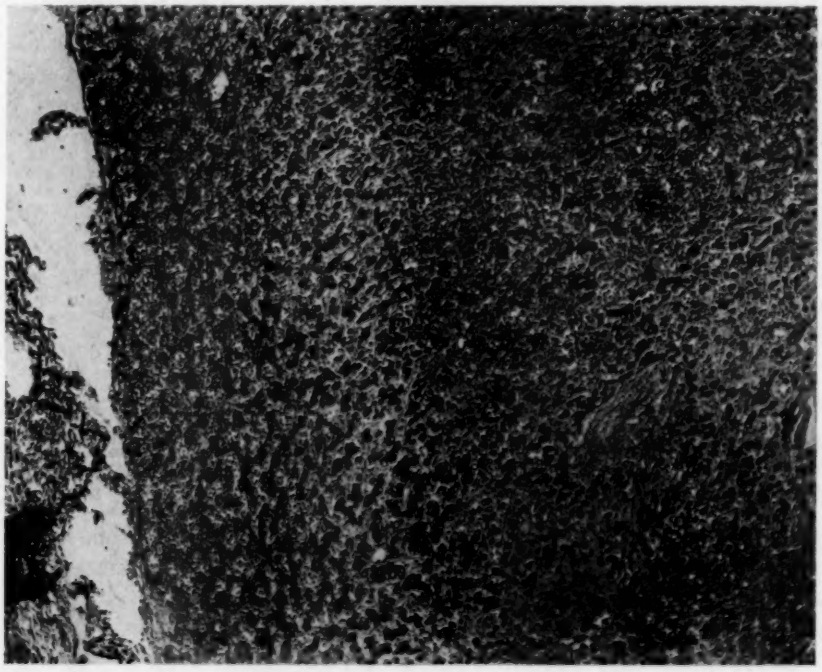

Fig. 3.—Section of liver showing complete loss of the normal architecture as a result of necrosis; hematoxylin and eosin; × 85.

A hematoma of the scalp was present over the right frontal and parietal bones. The occipitoparietal suture on the right side was widened for about 3 cm., and on the left side the parietal bone overrode the occipital bone for about the same distance. The fontanels were neither depressed nor bulging. A small hemorrhage was present in the trapezius muscle on the left side. The brain and the attached spinal cord were removed inside their intact dura. There was an extensive ragged tear of the right leaf of the tentorium cerebelli, starting posteriorly in front of the transverse venous sinus several centimeters to the right of the junction of the falx cerebri and tentorium and continuing anteriorly and medially to the junction of the vein of Galen and the straight sinus. An extensive subtentorial hemorrhage surrounded the pons and lay on the superior surfaces of both cerebellar lobes. Hemorrhage was also present intradurally the entire length of the spinal cord.

Summary of Observations at Necropsy.—The anatomic diagnosis in this case may be written as follows: tear of the tentorium; subtentorial hemorrhage; hemorrhage into the suprarenal gland (left); hypoplasia of the hepatic artery; thrombus in the portal vein; infarct of the liver.

The cerebral accident, as well as the hemorrhage into the suprarenal gland, are frequent observations in difficult deliveries and do not concern us here. Actual tears into the parenchyma of the liver during breech deliveries have also been described,[46] but there was no tear demonstrable in the liver of this patient. With an enfeebled arterial circulation due to the hypoplastic hepatic artery, and a complete absence of venous blood because of the thrombus in the portal vein, the infarct of the left lobe of the liver seems to be explained. That the right lobe did not suffer similarly is difficult to explain other than by the possibility that the phrenic arterial-subcapsular anastomoses may have been adequate. No explanation for the thrombus in the portal vein is available.

SUMMARY

Traumatic injuries to the liver resulting in necrosis, even when associated with thrombosis of large branches of the portal vein, are not examples of true infarcts of the liver.

Occlusion of the portal vein in the presence of an adequate arterial blood supply does not produce infarcts of the liver, but may produce an atrophy which is often misnamed "atrophic red infarct."

Occlusion of the branches of the interlobar portal vein produces infarcts of the liver.

Necrosis of liver cells due to occlusion of the hepatic veins is not an example of infarct of the liver in that the interference in these cases with the blood supply to the liver is only an indirect one.

Complete block of the arterial blood supply to the liver always leads to infarction, even in the presence of the full venous circulation by way of the portal vein. When infarction fails to take place, it is due to an efficient collateral arterial circulation by way of: (*a*) the right gastric or gastroduodenal arteries, (*b*) the artery in the ligamentum teres, (*c*) the phrenic anastomoses, (*d*) the arteries in adhesions between abdominal viscera and the liver capsule or (*e*) anomalous arteries to the liver.

Twenty-seven cases of infarct of the liver collected from the literature are listed in chronologic order. Of these, three cases quoted by Narath are based only on clinical observation, in each instance the patient having made an eventual recovery.

Finally, an original example of infarct of the liver is reported.

46. Green, H.: Hemorrhage of the Liver as a Cause of Death in the New-Born, Arch. Pediat. **43**:627, 1926.

General Review

THE MICROBIC ETIOLOGY OF RHEUMATIC FEVER AND ARTHRITIS*

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In grouping together rheumatic fever and arthritis in any study, serious difficulties are sure to arise. Moreover, clinical and etiologic evidence to the present have failed to develop any hard and fast line of demarcation between these conditions. It is not proposed to discuss the clinical features more than to refer to the difficulty involved in differentiation of some of the borderline cases, which all will readily admit. This clinical confusion has to some degree been carried over into the etiologic investigations, and it is now an almost impossible task to separate entirely the bacteriologic studies of rheumatic fever and of arthritis.

Many theories of causation have been proposed, and for rheumatic fever and some forms of arthritis especially, most have involved, in the last analysis, a conception of infection with pathogenic micro-organisms, though other factors, such as trauma in arthritis, are generally recognized. Cause and effect are frequently difficult to differentiate, and noninfectious etiologic possibilities cannot as yet be eliminated, but at least in regard to rheumatic fever, the known clinical and epidemiologic facts point to this condition as an infectious disease.

The space available for this paper prohibits any claim to exhaustive consideration of all the literature in this complicated field. Indeed, such consideration is felt to be unnecessary because of the reviews of the early work by Poynton and Paine, Loeb, Bulloch and others, and inclusion of the more recent work in such monographs as those of the Pickett-Thomson Research Laboratory.[1]

Undoubtedly the most impressive bacteriologic evidence, though not perhaps the earliest, relates to the presence of streptococci in rheumatic fever. These observations, naturally, center around the isolation of micro-organisms from the tissues of patients. Triboulet and Coyon (*b*) and Apert isolated pleomorphic diplococci from the blood of several

* Submitted for publication, Jan. 29, 1930.
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1. See Thomson and Thomson in the bibliography appended.

living patients with acute rheumatism and endocarditis and several bodies post mortem. Westphal, Wassermann and Malkoff isolated from the blood post mortem a streptococcus that produced a nonsuppurative multiple polyarthritis in rabbits, but did not state that they considered this organism the cause of rheumatic fever. Soon afterward, the researches of Poynton and Paine, Beattie, Beaton and Walker, Coombs (*a*), Walker and Ryffel in England and others resulted in numerous isolations of a micrococcus from various cultures from tissues of patients with rheumatic fever. Tonsils, pericardial fluid, heart valves, cerebrospinal fluid, appendix and blood both ante and post mortem yielded micrococci, the microscopic and cultural characteristics of which were variously described. In spite of the fact that many of these isolations were from postmortem material and from relatively few living patients, the micro-organism was for the most part in each instance considered specific and believed to be the cause of rheumatic fever. A healthy note of scepticism was, however, sounded by Lewis and Longcope, by Philipp and by Cole. The former said:

> In view of the fact that streptococci isolated from sources other than the blood or complicating lesions from cases of rheumatic fever do, under certain circumstances, produce arthritis and endocarditis in animals when injected intravenously, it is surprising that the English observers, particularly, have made so few experiments to control their work.

But they concluded that a streptococcus which they isolated from a fatal case of rheumatism, endocarditis and chorea "is the same as that described by Wassermann, Meyer, Poynton and Paine, and Walker." Philipp failed to find organisms in any of his 21 blood or 6 synovial fluid cultures from rheumatic fever patients. This was apparently an extremely thorough piece of work. Cole stated as purely negative evidence, that all his attempts to grow organisms from the blood and joints in acute rheumatic fever failed. Although taken altogether these early cultural results were impressive, the high percentage of postmortem isolations, particularly in view of the more recent studies of postmortem bacteriology, makes the value of this type of evidence doubtful. Epstein and Kugel found nonhemolytic streptococci in blood, bone-marrow, heart muscle or valve in 86 per cent of their routine postmortem examinations. They concluded "that no significance can be attached to the recovery at necropsy of such organisms as *Streptococcus alpha, Streptococcus gamma, Enterococcus, Staphylococcus aureus, Bacillus coli* and *Bacillus pyocyaneus* unless the same organism has been found during life." Slightly less condemnatory of postmortem bacteriology are Hunt, Barrow, Thompson and Waldron who, working independently found positive postmortem blood cultures in 31, 43.7, 24 and 20.7 per cent of cases, respectively. In every case but one in which

blood cultures were positive, foci of infection were found. They concluded that postmortem bacteriology is reliable and often leads to the solution of the exact cause of death. Postmortem bacteriologic observations of this nature make it appear doubtful that convincing cultural evidence of the cause of rheumatic fever is forthcoming by necropsy studies alone.

Since the early bacteriologic isolations, there has been a steady succession of cultural studies of patients with rheumatic fever. Organisms supposed to be causative have been cultivated from tonsils, throat, blood, feces and synovial fluid usually of the living patient, and on account of cultural or immunologic characteristics have often been considered specific. Some of the organisms thus isolated have been described as follows: a coccus "closely related, but not identical with the coccus described by Poynton and Paine" by Frissell; three types of streptococci (from the joints) each readily convertible into the other by Rosenow (*c*); a diplostreptococcus usually anhemolytic and with constant morphologic and cultural characteristics from blood, tonsils and spinal fluid in chorea by Quigley; green, or hemolytic streptococci from the blood of two thirds of patients with polyarticular rheumatism by Freund and Berger; a short-chain nonhemolytic streptococcus with constant serologic and biologic reactions from the blood, tonsils and stools by Small (*a*), and Kreidler; three groups of streptococci from the tonsils and postnasal spaces of patients with acute and subacute rheumatism by Lazarus-Barlow; streptococci, usually of the viridans group, apparently not specific, from the blood by Clawson (*a*); and a nonmethemoglobin-forming streptococcus producing a specific exotoxin from the blood by Birkhaug (*a*). Recently Cecil, Nicholls and Stainsby (*b*) reported the finding in a high percentage of blood and joint cultures from patients with rheumatic fever, of streptococci predominantly of the alpha or viridans type and apparently falling into definite biologic groups. This array of observations, some agreeing and some conflicting, is difficult enough to interpret even without a considerable number of failures to isolate similar organisms. If one assumed that the organism isolated in each instance was causative, one would be forced to conclude either that rheumatic fever is not due to a specific micro-organism, but is a symptom complex known by that name which can be produced by any one of several types of organisms, or that the bacterium involved can readily change in morphologic, cultural and invasive qualities.

To complicate matters further, numerous others besides Philipp and Cole, apparently using extremely careful and often varied technic, have failed to find organisms similar to any of those described. Some observers also have found bacteria without demonstrating any valid differential or specific features. Loeb, who found diplostreptococci in

several of his blood and joint cultures, noted that they were in no way different from other strains. He said: "All the characters supposed to belong particularly to the coccus of rheumatism have been shown to occur in other strains as well." Harrison failed to isolate "streptococcus rheumaticus" from the blood of 26 patients. Swift and Kinsella did not succeed in cultivating organisms from the joints, and recovered nonhemolytic streptococci from less than 10 per cent of their blood cultures. They concluded: "No type of streptococcus has been constantly associated with acute rheumatic fever." Lynch and Irvine-Jones, following Clawson's technic, failed also to isolate micro-organisms from the blood stream during life. Nye and Seegal, using varied and apparently adequate methods, failed to find nonhemolytic streptococci in the blood of 25 patients with the disease. They recovered nonhemolytic streptococci from the throats of patients with the disease and from normal persons with about equal frequency, but found both types relatively nonpathogenic for rabbits. Neither Harrison nor Nabarro and MacDonald could observe any essential difference between streptococci isolated from rheumatic tonsils and those from nonrheumatic tonsils.

Positive observations are admittedly of greater import than negative ones, but if the cultural evidence of the specific nature of rheumatic fever is to prove important, future research should show a greater uniformity of results or some adequate explanation for the discrepancy recorded.

Experimentation on animals which has constituted a part of almost every etiologic study, has again resulted in a wide disparity of opinion. The earlier workers were, for the most part, intent on producing in animals, usually rabbits, by intravenous inoculation of the organisms that they isolated, a multiple nonsuppurative arthritis which should differ from the usual changes observed by similar inoculation of streptococci from other sources (Beaton and Walker, Poynton and Paine, Beattie, Beattie and Yates, Lewis and Longcope, Shaw, Westphal, Wassermann and Malkoff, and others). Cole, however, using seven strains of streptococci isolated from nonrheumatic sources, found that arthritis and endocarditis could be produced in rabbits by these strains. He concluded: "The description of a distinct variety or species of streptococci based on this property of causing endocarditis and arthritis is unwarranted." Opposed to this view were Coombs, Miller and Kettle, who said, "Such differences as exist between the experimental rheumatic infection and the human variety are accountable for by the difference in the mode of entry of the infective agent in the two conditions."

Gradually, largely as the result of an increasing number of reports of polyarthritis experimentally produced by the inoculation of many

types of organisms, it became recognized that the criteria of the animal equivalent of rheumatic fever were not wholly known and should be more carefully defined. This has involved serious difficulties, as the generalized nature of rheumatic lesions is only now becoming thoroughly recognized (Pappenheimer and von Glahn, Swift, McClenahan and Paul and others), and the translation of these physiologic and morphologic changes into the conditions observed in the experimental animals is subject to wide variation of opinion. Certainly, nonsuppurative polyarthritis and endocarditis are suggestive as equivalent changes, but because they have been produced by so many apparently diverse organisms something more seems necessary. The focal myocardial lesions described by Aschoff and called Aschoff bodies have been considered as practically pathognomonic of rheumatic carditis. These and similar myocardial lesions have been frequently described and discussed (Bracht and Wächter, Coombs (*b, c*), Pappenheimer and von Glahn, Thalhimer and Rothschild, Clawson (*b*) and others), but there does not appear to be any agreement as to what constitutes Aschoff bodies or their equivalent in the rabbit. Thus, Thalhimer and Rothschild said that "the only point of similarity between the experimental lesions and those found in cases of rheumatic carditis in man is their focalized nature." Miller also, in considering this question, stated that "in about one half of the rabbits and two thirds of the guinea-pigs myocardial lesions were encountered which consisted of interstitial accumulations of lymphocytes and endothelial cells. Similar lesions were found in control animals." Clawson, in a recent review of the Aschoff nodule, went even further and declared that "it is doubtful whether the Aschoff nodule should definitely be considered a specific lesion resulting from a specific rheumatic virus." This opinion is also held by Klinge. One can only conclude that no single feature of experimental rheumatic fever has been shown to be specific. The interpretation even of certain groups of lesions is doubtful, though Gross, Loewe and Eliasoph considered that the reproduction of Aschoff bodies, nonbacterial pericarditis and nonbacterial verrucous endocarditis afford essential criteria. It is evident that controversy over the specific nature of an experimental rheumatic fever can only come to an end when agreement can be reached as to what is meant by the lesions experimentally provoked. The ease with which arthritis can be produced in rabbits perhaps makes the general use of this animal in this disease unfortunate.

Mention must be made of the failure encountered by Miller in the attempt to transmit the virus from whole blood, serum, joint fluid, pleural fluid or throat washings of patients in the acute stage of rheumatic fever to rabbits and guinea-pigs. One may also note the failure of Gross, Loewe and Eliasoph to produce anything which they con-

sidered as analogous to rheumatic fever by injecting streptococci from various sources into a large number of animals of seven different species. Nye and Seegal found the nonhemolytic streptococci which they isolated from the throats of rheumatic patients relatively nonpathogenic for rabbits.

On the other side of the balance are large numbers of reports of experimental arthritis with or without other lesions produced by streptococci from various sources (Rothschild and Thalhimer, Lazarus-Barlow, Cole, Clawson, Jackson, Rosenow (*c*), Small, Kelly, Belk, Jodzis and Fendrick, Davis, Topley and Weir, Coombs, Miller, Kettle and others). The arthritis produced was sometimes considered a specific reaction to the organism isolated from rheumatic tissues, but most of those observers who controlled their work with streptococci from other sources obtained a similar reaction (Jackson, Davis, Topley and Weir and others). Of great importance in this experimental field are the observations of Schloss and Foster. To quote from their summary:

> Inoculation of cultures of *Streptococcus pyogenes* [hemolytic organism obtained from the tonsils of patients with rheumatic fever] into the blood stream of four monkeys induced a polyarthritis suggestive in certain respects of rheumatic fever in man. In three instances immunity to the infectious agent was observed after repeated inoculations. The infecting organism could be recovered from the blood stream at the onset of symptoms, but not afterwards. This fact possibly has some bearing on the failure to isolate organisms from the blood of man with "rheumatic fever." Recovery from the induced arthritis may be complete and in such cases no lesion is found in the joint or periarticular tissues at autopsy. . . . Agglomerations of specifically staining cells were noted in the heart muscle, kidney, liver, spleen, and periarticular tissues.

The difficulties involved in performing this type of experiment are perfectly obvious, but it seems that the barriers to human experimentation in this disease make it wise to investigate all the possibilities of experimentation in the species most closely related to man.

Various theories have been proposed in the attempt to explain the apparently conflicting clinical, bacteriologic and experimental observations. That which has received the most attention in recent years is the allergic theory, though suggestive observations along this line have been made now and again over many years. Menzer, in 1902, suggested that streptococci were distributed to the joints first without producing symptoms, but that inflammatory symptoms developed only after the elaboration of antibodies in the tissues. The allergic hypothesis received further analysis and observation by Weintraud, Friedberger, Herry and Faber. The latter, especially, working with rabbits, contributed significant observations. He found that by injecting *Streptococcus mitis seu viridans,* obtained by Libman from the blood of a patient with subacute endocarditis, into the joints of rabbits, these animals apparently

became sensitized to this organism in such a way that subsequent intravenous inoculation with this organism, and with this organism only, invariably produced arthritis. This sensitization could be developed only after three or more intra-articular inoculations. He therefore suggested an analogy between this phenomenon and the relapses in acute rheumatic fever. In a discussion, he stated:

> It seems to be clearly proved that this preparatory or sensitizing process is, within narrow limits, a strictly specific one; i. e., the organism used for the exciting, intravenous injection must be the same as that used for the sensitizing, intra-articular injection, else the reaction fails to occur.

This early work passed with relatively little notice for a time, but during the past five years has received considerable concentrated study. Zinsser, and Swift, Derick and Hitchcock and their colleagues, have been particularly interested in this aspect of the subject. The allergic problem has been attacked mainly from two angles; the study of experimental streptococcal allergy in rabbits, and the study of allergy in man as evidenced by reactivity to streptococcal antigens in skin tests.

The analogy between the onset and manifestations of rheumatic fever and those of syphilis and tuberculosis was early pointed out by Swift. This led to the consideration of rheumatic fever as perhaps similar to tuberculosis and syphilis in some aspects and requiring similar focalized primary sensitizing lesions which in human rheumatic fever might well be located in the tonsils. Swift, Mackenzie and Hanger, Hanger, Zinsser, and Kinsella and Hagebusch were chiefly responsible for the demonstration of corresponding phenomena in rabbits. It was found that when autolysates, filtrates or suspensions of certain nonhemolytic or green-producing streptococci were injected intradermally into rabbits, a type of skin reaction occurred which could be divided into definite phases depending on the state of immunity, normality or hyperergy (Swift) of the particular animal. Hyperergy can be produced in normal rabbits by continued intradermal injections of streptococcal antigen. The animal is then subject to dermal, ocular or lethal reactions of much greater severity from a relatively small amount of stimulating antigen than is a normal animal. This state can be maintained, however, only by continuing the intradermal focal sensitization. Type specificity was not, as a rule, observed. The state of immunity could be produced from normal or hyperergic conditions by intravenous injections of the streptococcal antigen; in this way, the reaction of the rabbit to the antigen was markedly reduced in intensity. Analogy, therefore, can translate this picture into rheumatic fever in man, with the tonsil serving as the primary focal sensitizing lesion for an antigen perhaps common to streptococci which have heretofore been considered distinct.

The evidence thus far advanced for this theory is based on animal experimentation alone and can be applied to rheumatic fever in man only by analogy. Zinsser and Yu summed the matter up in the following manner:

> It seems to us possible that the curious frequency with which non-hemolytic streptococci are associated with the disease, while at the same time the non-hemolytic streptococci so found represent many varieties, may be due to the fact that with these organisms that peculiar balance between invasiveness and resistance is established in man, which most easily results in chronic infection.

Skin tests with streptococci or their products made on patients with rheumatic fever, convalescents and control groups have been interpreted as bearing directly on the allergic theory. Birkhaug, Lucas, Kaiser, Hart and Irvine-Jones have made studies of this nature. Birkhaug (*c*), as a result of 3,114 skin tests divided among 42 patients with active rheumatic fever, 146 patients with inactive or "cured" rheumatic fever, 69 patients with chronic arthritis and 337 nonrheumatic controls, concluded:

> It appears that a non-specific common allergenic factor is present excessively in the bacterial products of indifferent and viridans streptococci and moderately present in solutions of hemolytic streptococci, to which cases with either acute rheumatic infections or chronic infectious arthritides react hyperergically.

Irvine-Jones suggested similarly "that the rheumatic syndrome is an allergic response of certain predisposed persons to the common streptococci of the upper respiratory tract." Kaiser found no parallelism between the skin tests with the filtrate from the cultures of streptococci isolated by Birkhaug and the Schick and Dick tests, but Hart did not believe that it was clear whether the reaction obtained with this test is purely an allergic phenomenon as in the tuberculin test or whether it indicates a susceptibility as in the Schick and Dick tests.

The skin tests so far made have been with preparations from streptococci only, and are hence subject to the criticism of inadequate control, though the results are certainly suggestive. In conclusion, it can be said that the experimental support of the allergic theory already obtained opens a field which may aid materially in explaining the mechanism of infection in rheumatic fever. It does not seem that the essential conception of rheumatic fever as a disease caused by pathogenic microorganisms will be altered, though many as yet obscure features may be explained by further studies along this line.

Closely related to the studies on allergy have been those involving a consideration of a soluble bacterial toxin. Again, the conception of a toxic agent has resulted largely from the high percentage of failures to isolate bacteria from the joints or from attempts made to explain the

mechanism of action. Though not a wholly novel suggestion, the question of toxin production has received most attention during the last few years. Birkhaug, Kaiser, Steinfield and Jacobs, and Hart have described and employed a soluble toxin from various streptococci isolated from patients with rheumatic fever. Rheumatic persons showed relatively high susceptibility to these toxins (generally prepared as a Berkefeld filtrate), as measured by skin reactions. In some instances, animals showed marked toxic effects from intravenous or intra-articular inoculation. A further extremely interesting observation was that of Birkhaug (*a*) following intravenous inoculation of himself with such a filtrate. He employed for this purpose a strain of nonhemolytic streptococci isolated repeatedly from a patient with rheumatic fever. About twenty-four hours after the injection acute multiple arthritis developed with fever, pain, swelling and redness. This condition subsided in a few days. Birkhaug's description of the course of events is so striking as to make repetition of the experiment on a larger scale highly desirable, if other self-sacrificing volunteers can be found.

Irvine-Jones observed that persons suffering from rheumatic fever showed a marked sensitivity of the skin to filtrates of widely diverse streptococci from normal as well as from rheumatic subjects. Lazarus-Barlow found no exotoxin associated with the streptococci that he isolated from the tonsils and postnasal spaces of patients with rheumatic fever, but believed that there was evidence of an endotoxin which stimulated the production of antitoxin and affected the heart muscle, lungs and other organs of rabbits. Nye and Seegal found, with few exceptions no soluble toxins giving rise to the skin reactions comparable to Birkhaug's test toxin, in the nonhemolytic streptococci that they isolated from the upper respiratory passages. The study of toxins in relation to rheumatic fever is hampered by the multiplicity of streptococci which have been found, but again it is possible that extension of these studies may throw considerable light on the specificity of the streptococci involved.

Before passing to the consideration of streptococci in arthritis, it must again be stated that no thoroughly satisfactory classification exists. This is reflected on clinical grounds by a frequent tendency on the part of the disease to change from acute to chronic, from multiple joint involvement to involvement of a few or single joints, and even sometimes from nonbony changes to osteoarthritis. In fact, the clinical gradations between acute rheumatic fever, on the one hand, and chronic osteoarthritis on the other are so close together that they sometimes involve great diagnostic difficulty. Even pathologic studies do not provide an invariably satisfactory basis for classification. That differences between types exist can scarcely be doubted, but even thorough anatomic

studies of joint disease have failed to yield a classification valuable in directing the clinician in the course he must pursue. Etiologically, too, the classification even at the extremes is not distinct, since streptococci and other organisms have been found in tissues from all types of joint disease with as yet no valid differential features. This confusion has been noted by many and is well expressed by Elliott:

> If such a pathological picture is accepted for so-called rheumatic fever, then it would seem but a step to enter the field of chronic polyarthritis—depending upon the attenuated or mutated organism acting. We have, however, no such proof limiting the chronic types of arthritis to a single organism, as in rheumatic fever. On the contrary, there is much pointing to the probability of its multiple origin from many germs.

As in the case of rheumatic fever, however, streptococci of various sorts have been more frequently implicated in arthritis than other organisms. Attempts to isolate micro-organisms from the tissues in arthritis have been fraught with even more complications than in rheumatic fever, since the conception of focal infections has stimulated the isolation of micro-organisms from a greater variety of tissues.

One of the earliest definite bacteriologic reports on arthritis was that of Poynton and Paine,[2] who at necropsy found a diplococcus in the synovial membrane of the knee joint of a man, aged 67, several of whose joints showed the chronic destructive changes recognized as occurring in one type of rheumatoid arthritis. On two occasions, when injected into rabbits, it produced a severe arthritis, but no cardiac lesion. This arthritis differed in type from that which they had hitherto produced with the diplococcus of rheumatic fever. They believed that this diplococcus was the cause of the arthritis in the case from which it was isolated. Forkner, Shands and Poston cultivated the synovial fluids from 63 persons who had "chronic infectious arthritis" and found that fourteen were positive. Eleven of these positive fluids yielded *Streptococcus viridans,* two *Gonococcus* and one *Staphylococcus aureus.* Cecil, Nicholls and Stainsby found attenuated hemolytic streptococci in a number of cultures from joints of patients with "chronic infectious arthritis." Sekiguchi and Irons in cultures from joints of swine with chronic arthritis obtained a high percentage of mixtures of minute bacilli and streptococci, but believed that the latter were usually secondary invaders. Bacteriologic studies on arthritis in lower animals may prove of some aid in solving the problem in man.

As in rheumatic fever, the question of bacteremia in arthritis has developed investigations based on blood culture methods. Moon and Edwards, using a somewhat complicated blood culture technic, concluded:

2. Poynton and Paine: Page 149.

In arthritis, pararthritis, and myositis, organisms may be isolated from the blood stream by improved cultural methods, This is possible more frequently in the acute stages when the patient is in a febrile condition, and less frequently in the subacute and chronic stages of the infection. Streptococci may frequently be cultivated from the blood stream in rheumatoid arthritis. There is evidence that the so-called diphtheroid bacilli and bacillus mucosus occasionally cause infection of the joint structures.

Richards obtained *Streptococcus viridans* from the blood in 14 of 104 cases of chronic arthritis. Hadjopoulos and Burbank, by neutralizing the alexin in the blood of patients suffering from chronic arthritis, obtained a high percentage of positive cultures in the fall and winter months. Streptococci predominated, but diphtheroids and *Staphylococcus aureus* were also found. Surányi and Forro obtained 68 per cent positive cultures from 25 patients with polyarthritis. The organisms all fell into the nonhemolytic or the green-producing class, though apparently no attempt was made to place them more accurately. Cecil, Nicholls and Stainsby made blood cultures in 78 cases of "chronic infectious arthritis" with positive results in 61.5 per cent. Of the streptococci recovered, 83.3 per cent were culturally and biologically identical and appeared to be attenuated hemolytic streptococci. The remaining 16.7 per cent fell either into the *viridans* or the indifferent group. Diphtheroids were obtained in a few instances.

Lymph glands draining involved joints were excised aseptically and cultured by Rosenow (*b*), Forkner, Shands and Poston, Gibson and Poston. Rosenow isolated organisms in 35 of 38 cases divided as follows: streptococci 14, streptococcus-like anaerobe 9, *Bacillus welchi* 9, *Staphylococcus* 3, *B. mucosus* 1 and *Gonococcus* 1. In no instance were the streptococci hemolytic, and often there was a marked difference between the organisms isolated from lymph glands and those found in foci of infection. Forkner, Shands and Poston obtained 10 positive growths from 21 lymph gland cultures. Nine of these were *Streptococcus viridans* and 1 was *Gonococcus*. In 5 of these cases, the same type of organism was grown also from the joint. More recently, Poston has studied 120 lymph glands by cultural methods and obtained organisms in 72 (60 per cent). *Streptococcus viridans* was recovered 67 times, *Streptococcus nonhemolyticus* twice, *Staphylococcus aureus* twice, and *Gonococcus* once. It would be valuable to control this work with normal lymph glands and glands enlarged in other diseases to a greater extent than has apparently been done in studies of this condition.

The relation of organisms isolated from foci of infection to the morbid process elsewhere is one of extreme difficulty, since in so many instances a number of different types and strains can be obtained from the same source. Nevertheless, the doctrine of focal infection as

elaborated particularly by Billings, Rosenow [3] and others has received wide attention, and has been studied exhaustively. The tonsils have been subjected to much bacteriologic study in chronic arthritis probably partly because of the apparent relation of tonsillitis to rheumatic fever. Experiments have utilized a variety of methods from simple cultivation of organisms from the tonsil in situ to quantitative bacteriologic methods and experimental lesions in laboratory animals. Hence any comparison of results of different observers is fraught with great difficulty and further complicated by its relationship to the "elective localization" postulated by certain workers. Rosenow, Davis, Byfield, Rhoads and Dick and a host of others have reported the recovery of streptococci from the tonsils of patients with various types of arthritis. The streptococci described have been of all types as far as reaction on blood is concerned—green-producing types perhaps predominating, but indifferent and hemolytic types being frequently described. Polvogt and Crowe examined tonsils removed from 10 patients with chronic tonsillitis and infectious arthritis and found hemolytic streptococci "in almost pure culture" 8 times and *Staphylococcus aureus* twice. Rhoads and Dick observed a high percentage of tonsil remnants in "tonsillectomized" patients, and made quantitative bacteriologic tests of tonsils or tonsil remnants removed surgically. They found streptococci of all blood reactions and some other organisms, at times, in the tonsils from arthritic patients as well as in those from patients suffering from other conditions. When these streptococcal strains were injected into rabbits, the most frequent lesion found at autopsy was arthritis. The rôle of the tonsil in harboring the infectious agent in some cases of arthritis is almost beyond dispute, but what exactly this agent is or the mechanism by which it acts is as yet not accurately determined.

Streptococci have also been obtained from dental abscesses or pulpless teeth from patients with arthritis. The work of Rosenow and Ashby, Rosenow (*d*), Price, Willcox, Franke, Hurst, Haden, Watson-Williams, Davis, Meisser and Brock and many others has done much to establish the facts of dental focal infection. Unfortunately, the same lack of uniformity in the type of streptococci isolated has provoked a sense of confusion and futility difficult to surmount. Nevertheless, streptococci have been found, often in pure culture, in dental foci; removal of these foci has resulted in clinical cure so often that indirect evidence of their causative connection in some instances seems convincing. The hypothesis of "elective localization" advanced by Rosenow has perhaps received its greatest support in the study of dental streptococci. This hypothesis involves the conception of an affinity

3. See many papers published from 1910 on in the Journal of Infectious Diseases, the Journal of the American Medical Association, etc.

of some organisms for definitely selected organs or tissues of the body. The assumption of fixed properties of invasion for these streptococci is necessary for this theory and a recognition of groups of streptococci differentiated on the basis of their ability to produce arthritis, nephritis, myocarditis, duodenal ulcer and so forth. Rosenow and his followers and recently Precht have succeeded in producing arthritis alone in rabbits or dogs when streptococci from arthritic patients were used and nephritis or ulcers of the stomach alone when streptococci from homologous sources in man were employed. Altogether, such a mass of evidence has been collected on this subject both pro and con, many having failed to substantiate these results of elective localization, that the only possible position at present is to suspend judgment. Holman, who recently reviewed the subject of focal infection and elective localization, said:

> Does the localization of bacteria such as streptococci depend on an inherent property in the microorganism which is independent of, or which is demonstrable in spite of, alterations of technic or varying susceptibilities due to different species of animals, the effects of diet, previous or concurrent spontaneous infection, age, and a variety of environmental conditions? Each possible factor must be controlled independently, and it is a difficult undertaking. . . . However, what Rosenow and his followers particularly showed and what all the other investigators of the problem have definitely demonstrated is that streptococci do localize in various organs and tissues and can produce lesions at least sufficiently suggestive of those found in man so that their potential danger in infected foci cannot be neglected.

Streptococci, as well as many other organisms, have been recovered from numerous other tissues of the body and often have been deemed causally related. Accessory nasal sinuses, gallbladder, cervix, urine, prostate and feces have served to provide streptococci for those working on cases of arthritis (Watson-Williams, Wilkie, Moench, Kauntze, Culver, Wear, Keating and Mutch). The organisms thus obtained have been studied in different degrees, varying from the determination of the effect of removal or treatment of the focus on the course of the disease, to experimental production of the disease in animals and serologic tests. In general, except for certain of the serologic tests, to be discussed later, the same statements apply as were made in considering the significance of streptococci from other infected foci.

Streptococci obtained from practically all these sources have been shown to produce arthritis in animals. In some instances, the streptococci were given intravenously, in others intra-articularly, and in others they were inoculated around the teeth in an attempt to reproduce the infective focus (Livingston). Acute reactions have resulted even after the injection of moderate doses of dead autogenous streptococci (Davis [*c*]). In fact, joint reactions to streptococcal antigens from

so many different sources have been produced so readily, that this fact alone casts considerable doubt on any conception of a specific arthritic streptococcus (Harding, Nathan). Davis (*c*) said:

> The mere fact that the various strains of streptococci from the tonsils can cause joint-lesions in animals is perhaps in itself not of great significance. . . . Indeed, hemolytic streptococci from the normal throat may do so, as I have myself demonstrated. . . . It is possible that the reason why in one individual streptococci cause arthritis, and in another nephritis lies in the varying local susceptibility of the organs of the individual rather than in any peculiar specificity of the infecting cocci.

As is the case with rheumatic fever, the multiplicity of bacteriologic observations in arthritis has stimulated a search for some rational basis of explanation. Serologic differentiation early received attention through the work of Hastings. As a result of complement-fixation tests on streptococci, he stated:

> One is justified in concluding that *Streptococcus viridans* is an infectious agent and excites the production of a complement-fixing substance in the organism in cases of arthritis deformans, and, therefore *Streptococcus viridans* is the probable causative agent of the disease in many cases of arthritis deformans. Probably 40 per cent and more of cases of arthritis deformans should be considered as chronic infective deforming arthritis. Rarely the clinical manifestations of arthritis deformans may be due to gonococcus infection. The serum from one case may react positively to two different organisms, most frequently to *Streptococcus viridans* and to *Gonococcus,* when the reaction to the former should be considered the indicator of the causative agent, since with the latter, infection is often latent in the genito-urinary tract. Incidence of gonococcus infection is high and the clinical manifestations of arthritis deformans are rarely produced by gonococcus infection.

More recently Burbank and Hadjopoulos in a number of papers have described a technic for bacterial fixation of streptococcus types whereby various arthritic and rheumatoid conditions may be classified serologically into three major groups. These groups they described as:

> (*a*) Arthritis reacting to hemolytic streptococci and belonging to the iso-atrophic class. This type in pure form is periarticular.
>
> (*b*) Arthritis reacting similarly to hemolytic streptococci, but of different fixing properties. This type is aniso-atrophic or deformans.
>
> (*c*) Arthritis reacting to streptococci of the *S. viridans* type and belonging to the osteo-arthritic or productive form.

They go even further in this differentiation, saying:

> A fair percentage of arthritic patients, especially those suffering from colitis and chronic constipation, have a marked tendency to effect complement fixation in certain strains of nonhemolytic streptococci isolated from the intestinal tract of similar arthritic cases. This type of organism seems to be a transition form of *Streptococcus hemolyticus,* with certain properties lost through secondary intestinal implantation.

The vast scale on which this work has been done together with the confirmatory evidence of Green, who also found *Streptococcus viridans* and *Gonococcus* predominating in serologic tests, entitles this differential method to serious consideration. Hitchcock, in studying a large group of indifferent streptococci serologically, found a homologous group which he designated type I, though he feels that further division into subtypes is possible. The remaining strains he placed in group 10 because of their failure to react strongly with type I serum. This he believes is a heterogenous group. He found, however, that:

> Indifferent streptococci occur in comparatively the same abundance in the throats of patients suffering from rheumatic fever or early in convalescence from the disease as they do in those who have recovered from the disease, or in those patients suffering from other diseases. Type I occurs with comparatively equal frequency and abundance in the throats of all four classes of individuals studied.

Others in their attempts to classify and differentiate streptococci obtained from arthritic patients have employed various criteria. Solis-Cohen and Loewe have made use of a method which they term "pathogen selection" and which is an avowal of their belief that many different organisms may cause arthritis. This method is based on the essential conception that a patient with arthritis does not contain in his blood the immunologic properties to the particular organism causing his disease and hence his blood will allow that organism to grow whereas other organisms to which he is presumably immune are inhibited. The technic of this method, as described by Loewe (*a*), is as follows:

> An equal quantity of any specimen to be examined is inoculated, as far as possible simultaneously, on to suitable media on the one hand, from which after incubation, will be obtained the ordinary direct or "A" cultures, and on the other hand, into 5 cc. of the patient's own blood freshly drawn, which, after incubation and subsequent subculture on to similar media, will provide the pathogen selective or "B" cultures, according to whether the patient's blood happens to be able to inhibit, or otherwise, any or all of the bacteria shown by the "A" cultures to have been present in the specimen.

Frequently, by this method, more than one organism was demonstrated to be pathogenic for an individual, and frequently, also, more than one focus contained organisms deemed by this method to be pathogenic. This theory is difficult to reconcile with the delicate balance existing between infection and immunity. This balance would point more toward periods when the patient's immunity would be reflected in the inhibition of the growth of the causative microbe, as well as the others.

The possible occurrence of streptococcal allergy as explaining the mechanism of streptococcal arthritis enters this study, as well as that of rheumatic fever. It is obviously just as reasonable to consider

allergy as the important mechanism in the production of arthritis as in rheumatic fever. No great amount of observation or experimentation has been directed toward arthritis from this point of view, though the possibility has been suggested practically from the beginnings of this theory (Zinsser, Swift, Small [*c*]). Freiberg, however, claimed to have produced by the repeated injection of a bacterial extract an experimental arthritis in rabbits simulating the proliferative arthritis in man. This, he believed, is a local allergic manifestation of a generalized state of allergy to a specific bacterium or bacterial extract.

The presence and action of a soluble toxin are again difficult to determine because of the number of organisms that have been found associated with arthritis. In this connection, however, the observation of Fisher is of special significance. He deduced as the result of the intra-articular injection into rabbits of a few cubic centimeters of sterile human synovial fluid (from an osteo-arthritic joint) with the production in the rabbits of degenerative changes in the articular cartilage, that some kinds of joint fluid contain a toxic substance but no bacteria.

Streptococci, then, have been found associated with many cases of arthritis of various types, as well as with rheumatic fever. This association while not constantly noted by all observers has occurred sufficiently often to suggest a causal relationship in some instances, at least. Though no uniformity of type has been established for all such streptococci, two possible explanations are compatible with this etiologic interpretation, viz., that arthritis can be caused by streptococci of many types, not specific, or that the streptococcus of arthritis has many inconstant features (Davis [*d*], Rosenow [*a*]). The doctrine of microbic dissociation, as developed by Hadley and others, may serve as the ultimate explanation for such apparent inconsistency.

Although recent opinion has veered in the direction of the etiologic significance of streptococci, importance has been attached by various observers to certain other organisms both for rheumatic fever and for some forms of arthritis. Of these, undoubtedly the most important historically in its relation to rheumatic fever is the Achalme bacillus.

This organism was obtained by Achalme only by anaerobic cultural methods from the blood, pericardial fluid and other tissues post mortem. About the same time, this work obtained confirmation by Triboulet and Coyen (*a*), and Thiroloix; the latter, however, carried his studies of this organism further and found that growth could be obtained aerobically after several generations on milk and broth. When injected intramuscularly into guinea-pigs, the organism produced a serosanguineous edema, but had no effect on dogs or mice. In view of subsequent observations, Thiroloix' remarks are significant: "Il peut provoquer

des infections secondaries streptococciques" (It can provoke secondary streptococcal infections).

By early failures to corroborate the finding of this organism, and later neglect in attempting to find it, this etiologic theory has fallen into the limbo of lost causes. Recently, however, this microbe has again been brought into the limelight by Bertrand, who said:

> Seventeen years of uninterrupted research work upon the specificity of acute articular rheumatism, has convinced me that this affection is due to the anaerobic bacillus, described by Achalme thirty years ago, and studied later by Thiroloix, Rosenthal, Triboulet, and many others, but which has now dropped into obscurity through official indifference. In my opinion, inefficient technique in isolating this microbe, was above all, the cause of the lack of credit accorded to it. This polymorph microbe can assume the coccic form; on more than one occasion, I have witnessed the transformation of these two forms one into the other, in vitro as well as in vivo by intramyocardial inoculation of rabbits.

Bertrand also believed that chronic rheumatism is caused by this organism and stated that Vivien and Lautier, as well as himself, had been successful in the treatment of such patients with antirheumatic vaccine prepared from this organism.

What the final conclusions concerning the Achalme bacillus will be it is, of course, impossible to say. The evidence of its association with rheumatic fever or arthritis is certainly less convincing than that of the association of the streptococci with these conditions, though in view of the wide field opened by the newer studies of transmutation and dissociation it may prove in time that the Achalme bacillus has just as much relation to rheumatic diseases as have the streptococci.

Bacilli apparently other than that described by Achalme have been found in the tissues of patients with rheumatic fever or arthritis at various times. Probably the earliest of these was Schüller's bacillus. This was described by Schüller as a short bacillus with bipolar bodies and associated with single round cocci which he obtained from the periarticular structures in chronic arthritis. It was gram-negative and grew with difficulty at first on the usual laboratory mediums. When injected into rabbits' joints in fairly large quantities it never produced pus, but did produce chronic joint changes. It could be isolated again from these disordered joints. A similar organism was found a few years later by Blaxall. His observations were summarized as follows:

> (1) In the synovial fluid of eighteen cases of rheumatoid arthritis an organism has been demonstrated which is constant in its characteristics. (2) The organism is a minute bacillus exhibiting marked polar staining. It is difficult to stain and easily decolorized. (3) The organism can be grown in culture media and presents striking characteristics. In beef broth it gives the appearance of gold dust and on agar-agar and serum its growth is almost invisible. It does not grow on nutrient gelatin at ordinary temperatures. (4) It is present in the blood in severe

cases. (5) It has not been found in the synovial fluid from distended joints due to other causes. . . .

Fayerweather obtained short bacilli from joint cultures in four cases of arthritis. These bacilli were somewhat but not entirely alike, and he was unable to identify them with any previously described. By inoculation of these bacilli directly into the joints of rabbits, arthritis was produced. Intravenous inoculation had no effect on the rabbits. Goadby isolated organisms from the gums and other tissues of patients with "rheumatoid arthritis," which he believed were "streptobacilli" with bipolar staining "though very difficult to tell from streptococci." Nye and Seegal, although failing to find streptococci in blood cultures from 25 patients with rheumatic fever, recovered small gram-positive bacilli from two cases and in one of these from two cultures from the same patient. No important significance was attached to these organisms. Cecil, Nicholls and Stainsby in blood cultures from patients with "chronic infectious arthritis" isolated most frequently a type specific streptococcus, though in several instances they obtained "diphtheroid" organisms. Key in 29 positive cultures from 88 joint aspirations on 50 patients with chronic arthritis of all kinds obtained minute bacilli in masses or mixed with staphylococci, 14 times. These bacilli produced arthritis in rabbits when injected directly into the joints in 34 of 50 instances. Bacilli of these types have been frequently lumped together somewhat indiscriminately as "diphtheroids," and since similar appearing "diphtheroids" have been found from a great many sources they are generally considered as having no pathogenic significance. As streptococci, too, have been found from many sources, it is perhaps unwise to dismiss such bacilli without according them more study than they are usually allowed.

Staphylococci also have been considered by some observers to be the cause of arthritis of certain types. The foremost advocate of the staphylococci in this connection is Crowe, who believed in a dual etiology for arthritis, i. e., the streptococci as the cause of "osteoarthritis" and a specific white staphylococcus which he names *Micrococcus deformans* as the cause of "rheumatoid arthritis." If it is assumed that the differentiation between these forms of arthritis is accurate (about which, however, there is considerable doubt), the evidence for the staphylococci, as advanced by Crowe, rests chiefly on the following points—the isolation of a staphylococcus from the urine, feces or scurf of patients with "rheumatoid arthritis" which because of its type of growth on a special medium (Crowe's medium) and its agglutinative characteristics and the effect of vaccines on such patients is considered a specific type of staphylococcus differing from staphylococci found in other conditions or from other sources. A vast amount of work has evidently

been done by Crowe and others along these lines, but it is safe to reserve judgment until this work has been extended, particularly as far as original isolations are concerned, and confirmed by others. It is only fair to state that Crowe is not the only one who has collected evidence implicating staphylococci in arthritis. Thus, as early as 1893, Dor isolated an "attenuated staphylococcus" from the vegetations of the synovial membrane of a chronic arthritic joint which when injected intravenously into two rabbits produced an arthritis deformans of both knees. Crowe quoted Collins, Watson-Williams, and Watson as contributing evidence of staphylococcal infection in arthritis, particularly from the view of sinus infection. Mutch found pyogenic staphylococci in the small intestines associated with "chronic stasis" in patients with chronic arthritis. He stated:

> The suggested explanation of these phenomena is that ingested staphylococci sometimes escape destruction in the stomach, and, in their growth being encouraged by intestinal stasis, they infect the mucous membrane and surrounding tissues, and thereby produce morbid changes in the joints.

The comment by Poynton indicates, perhaps, too hopeless an attitude:

> It appears to me that, just as a particular streptococcus may cause acute rheumatism, so very possibly some staphylococcus may be an important cause of rheumatoid arthritis. Then I remember that the streptococcus of rheumatism, if cultivated in various solid media, may become indistinguishable morphologically from a staphylococcus, and I wonder whether in human diseases there is any essential line to be drawn between the streptococci and staphylococci.

Key, in addition to finding in chronically diseased joints the minute bacilli previously mentioned, found also staphylococci, either alone or mixed with the bacilli, in the majority of his positive cultures. These staphylococci when injected into rabbit joints produced arthritis in 66 of 84 cases—a slightly higher percentage than was found by inoculation of the bacilli.

A theory that intestinal protozoa, particularly the amebas, are responsible for a large group of chronic arthritides has been developed largely on the western coast of the United States. The evidence for this is largely due to the work of Barrow and Armstrong, Ely and his colleagues, and Kofoid. Amebas have been found by these observers in the stools of patients with chronic arthritis and in sections from necrotic areas of bone. The group in which such protozoan infestation is most common has been called by Ely (*a*) the great second type of arthritis, which he defines as having "two distinguishing clinical features: (*a*) bone production (lipping, spurring) at the joint line, and (*b*) absence (except in spinal involvement) of union between the ends of the bones, either fibrous or bony." This apparently is similar to the osteo-arthritis or hypertrophic arthritis of more common usage. Though

this form of arthritis is common in places where amebic infestation is believed to be rare, it is possible that this form of infection will prove a more important agent among the vast number of stimuli which are associated with arthritic disease. Others, e. g., Moorehead, have reported amebas also in association with arthritis. Moorehead's evidence was based on amebic dysentery and arthritis occurring coincidentally in soldiers with an improvement of both conditions following treatment with emetin. However, he does not report that he aspirated involved joints to search for amebas.

One other etiologic theory, this time affecting rheumatic fever, should be given brief consideration. Clarke suggested because of the peculiar geographic and seasonal distribution of rheumatic fever, which corresponds with certain habits of the common rat flea, *Ceratophyllus fasciatus,* that this insect is in some way connected with the etiology of the disease. While it is difficult to alter our views to accept this agent in such an important rôle, it must be admitted that Clarke has collected epidemiologic and entomologic evidence that should arouse considerable interest.

The etiologic theories for rheumatic fever and arthritis heretofore detailed form the basis for most of the studies which are being made at the present time to determine causation more definitely. Though there is practically no doubt that arthritis may in some instances be due to causes wholly nonbacterial (such as hemophilic arthritis), there have been numerous reports of types of arthritis occurring in other diseases. Certainly joint disorders are sometimes due to specific micro-organisms, and may be in some instances clinically indistinguishable from the types of arthritis the etiology of which is still subject to debate. This fact has been discussed a number of times, e. g., by Irons, Schottmüller, Coates and Gordon, Stockman, Milne, Umber, Le Noir and Liège, and there has been a gradual splitting off of these specific arthritides from the types the etiology of which is not known. That this process is not yet complete is evidenced by the continued reports of the specific nature of certain cases of arthritis.

To discuss tuberculous arthritis, one of the earliest to be differentiated from other forms of joint involvement, is not the purpose of this paper. Whether, however, typical tuberculous arthritis serves as the only relation between tuberculous infection and arthritic disorders has been questioned by several. Menzer (*b*) believed that latent pulmonary tuberculosis is a frequent cause of arthritis and that hence general measures for the improvement of the patient would do much more for the disease than salicylate therapy. Ascoli reported a case in which an "arthritis deformans" of the knee was evidently secondary to a tuberculous involvement. Platt similarly stated that "in adolescence

and in adult life infective arthritis often simulated tuberculosis. Operative exploration in knee joint conditions was often the most valuable diagnostic measure." Recently Wilkinson contended that many so-called cases of rheumatism are really caused by hidden foci of tuberculosis. He did not state that tuberculosis is the exclusive cause of such chronic inflammatory states, but believed that the symptom-complex hitherto associated with "rheumatism" may be the effect of tuberculosis.

The fact that infections with gonococci can cause arthritis of practically all types, both acute and chronic, is also too well known to discuss at length. Nevertheless there has been considerable direct and indirect evidence of late to indicate that many cases of arthritis not commonly classed as gonorrheal are, from an etiologic standpoint, of this nature. Thomas has discussed the clinical aspects of this condition and the difficulties in diagnosing the more chronic types after the acute initial infection has subsided. Pepper reported on three cases of gonococcal arthritis associated with old rheumatic endocarditis. He suggested that gonococcal focal infection may cause either a specific gonococcal arthritis or a nonspecific infectious arthritis and also that there is reason to believe that rheumatic infection prepares the soil not only for recurrences of rheumatic fever, but also for other types of arthritis, including gonococcal. From the bacteriologic point of view, the finding of gonococci from the lymph glands in "chronic infectious arthritis" by Rosenow (*b*), Forkner, Poston, and Cecil, Nicholls and Stainsby should be viewed as significant in this connection. It is undoubtedly true that a considerable percentage of at present undifferentiated cases of arthritis belong in the class of gonococcal infections. An attempt should be made to define the differential features more accurately.

Though syphilis as a cause of special forms of arthritis has long been recognized, e. g., Charcot joint, syphilitic arthritis per se when recognized still ranks as a rare enough condition to warrant case reports. Chesney, Kemp and Resnick reported two such cases characterized by subacute polyarthritis, enlarged tender lymph nodes and eosinophilia. Triturated lymph glands from both patients produced orchitis in rabbits from which *Spirochaeta* was recovered. Joint fluid from one patient produced similar orchitis in a rabbit, though no spirochetes were found in the joint fluids. Arthritis deformans of heredosyphilitic origin has been reported numerous times, recently by Ricciardi. Francisco also considered the importance of arthritis in congental syphilis, but stressed the point that in adults, especially, arthritis and syphilis occurring concurrently is not proof of the syphilitic nature of the arthritis, Stanojević reported a case of bilateral syphilitic sacro-iliac arthritis with the symptoms of periostitis. From the consideration of such case reports it becomes evident that differentiation of arthritis along this line has not progressed far.

It does not seem necessary to prolong much further comment on the numerous reports of arthritis occurring in or probably due to specific infections with known organisms. Holst, after reviewing the literature, described a spondylitis occurring in typhus fever which he believed was characteristic clinically and radiologically. Spondylitis as the result of typhoid fever is well known (Haselhorst, Kramer), and Barker suggested a broader view of typhoid fever as possibly responsible for secondary metastatic arthritis. Cases of arthritis due to paratyphoid infections have been reported by Madier and Ducroquet, Rowlands and Lewis. Arthritis of various types apparently due to the pneumococcus have been described numerous times (Carleton, Milch and Lepidus, Thomson and Thomson, and others). Kauntze obtained favorable results in treating patients with "rheumatoid arthritis, chronic rheumatism and allied diseases" with "autogenous" vaccines from coliform bacilli isolated from the patient's stools and agglutinated by his serum. Hill, Seidman, Stadnichenko and Ellis in 6 of 7 infections of the urinary tract with arthritis obtained pure cultures of the coli group from the urine. Four of these were *Escherichia* and 2 *Aerobacter*. Some relation between joint disorders and influenza has long been recognized and this has been recently discussed by Weil.

Unusual organisms have been occasionally recovered from patients with arthritis. Dick obtained *B. mucosus* (Friedländer's bacillus) repeatedly from the tonsils of a patient with multiple deforming arthritis of seven years' duration. Removal of the tonsils and the administration of autogenous vaccines produced marked clinical improvement. This organism produced arthritis in rabbits and dogs. Thjøtta and Gunderson in two blood cultures from a patient with "acute rheumatism with pleuritis, pericarditis and bronchitis" obtained a streptothrix. The third blood culture was sterile. Mutch and Mutch isolated *B. fallax* from a joint removed surgically from a patient with chronic arthritis.

Recently, occurrence of arthritis in undulant fever has come to be generally recognized. Arthritis is apparently so usually a concomitant of this disease that it is mentioned in nearly all clinical discussions; Von Mueller, Baker and Bierring, among others, discuss the clinical characteristics in some detail. Jensen speaks of a spondylitis from *B. abortus* infection.

COMMENT

In a large way, the problem of etiology of rheumatic fever and arthritis is one of the most important in medicine. The amount of disability from the joint involvement, cardiac damage and perhaps other complications is almost beyond comprehension. Add to that the suffering and the mental effect on the patient resulting from the usual hopeless outlook shared alike by medical men and the laity, and one has a subject

deserving intensive study. It is impossible to anticipate at what points the link in the chain of rheumatic disorders will be broken to allow more satisfactory treatment, but a determination of the etiologic factors at least offers the best avenue for the efforts of preventive medicine.

There seems to be little doubt that rheumatic fever and some forms of arthritis are usually due to infections with micro-organisms. That many different organisms can cause joint disorders in animals and in man seems also beyond the possibility of doubt. More than that has not been absolutely established. Rheumatic fever obviously offers the most favorable possibility for proving a specific etiologic agent, but it cannot be said that this has been done to complete satisfaction as yet. It may then well be asked on what basis one may consider the etiology as proved. Presumably, the answer to this question is in the satisfaction of Koch's postulates. This in its turn involves preliminary questions about which there also should be general agreement. The first of these is: What is meant by rheumatic fever? Is this limited by the textbook picture of acute rheumatic fever in children? Is acute polyarthritis in adults with or without tonsillitis and carditis included? In what category are growing pains in children with demonstrable endocardial damage placed? Or can these questions be settled only on the basis of the isolation of a specific microbe? These and other questions have perhaps not received sufficient attention in the bacteriologic studies directed at rheumatic fever. It is beyond the scope of this paper to attempt to answer these problems. To go further: From what tissues should the causative organisms be isolated? The clinical characteristics of the disease point to the joints, endocardium and tonsils with the question of the blood stream much in doubt. Yet organisms of different kinds have been isolated from all of these sources and several others, and have in most instances been considered causative. Other workers have failed to isolate organisms from these tissues, which they considered significant. Hence, it is questionable whether the bacterium or bacteria responsible for rheumatic fever are present in all of these locations for more than brief periods of time. In this connection, studies involving mechanisms, such as those on allergy or toxin production, may prove of especial value. Chances of contamination in tissue cultures are great, and the utmost care should be used in controlling technic. It must be also borne in mind that growth of organisms on artificial mediums over even a short period of time may alter their biologic, as well as their invasive, qualities. Finally, in considering reproduction of rheumatic fever, since this cannot be done in man (unless Birkhaug's experiment on himself points to a practicable way) the criteria constituting a satisfactory equivalent in lower animals should be agreed on. It seems reasonable to believe that such agreement is most likely to be reached

when species of animals closely related to man are employed for this purpose.

In forms of arthritis other than rheumatic fever, the problem seems of slightly different character. It is apparent that many agents both bacterial and of other nature may produce changes in the joints which are often as yet clinically indistinguishable. It is even possible that an organism also the specific cause of rheumatic fever may cause in adults, particularly, a form of arthritis which cannot be differentiated on clinical grounds from arthritis due to other etiologic agents. At least there is considerable basis for a belief that though there may be a large group of arthritic disorders due to specific organism or a closely knit group of organisms (with the streptococci indicated especially), microbes of many different kinds with primary locations in many different parts of the body are responsible for a certain percentage of the cases. It does not seem that this fact should prove too discouraging, since clinical and etiologic distinctions should offer considerably greater possibilities in prevention and treatment.

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Laboratory Methods and Technical Notes

A METHOD FOR DETECTING SPARSELY DISTRIBUTED TUBERCLE BACILLI*

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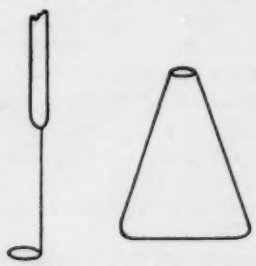
The principle of this method for detecting sparsely distributed tubercle bacilli consists in increasing the specific gravity of a given specimen by means of sodium chloride, allowing the preparation to stand and skimming off a surface area in which the bacilli are concentrated, by means of a large right angle loop.

The solid material (macerated if necessary) is mixed thoroughly with approximately 250 cc. of hypertonic saline solution (from 1.5 to 2 per cent) in distilled water free from acid-fast bacilli. Liquid specimens (e.g., urine or spinal fluid) are made up to a concentration of from 1.5 to 2 per cent by means of chemically pure sodium chloride. The solid suspension or liquid specimen is placed in a 250 cc. Erlenmeyer flask having a short narrow neck or preferably of the type resembling a truncated cone. The flask is then allowed to remain stationary at room temperature over night. When marked decomposition is feared, icebox temperature may be used. During the time that has elapsed, the tubercle bacilli (as well as some other organisms which may be present) will have risen to the surface,



Sketch of right angle loop and truncated cone flask.

where they may be picked up in films by means of a right angle platinum loop. This is merely a 10 mm. loop bent at right angles to the long axis of the glass rod and wire holder. By successively touching all portions of the narrow surface area in which the bacilli are concentrated, the entire area may be covered. Each film is transferred to a glass slide, dried in the air and fixed by heat. The usual method of staining is followed, and the finished slide is dried in the air.

Experimentally, it was found that a 4 mm. loopful of positive tubercular sputum suspended in 250 cc. of hypertonic saline solution invariably gave more positive results than a suspension of the same material in distilled water. Rather high saline concentrations failed to alter materially the microscopic appearance of the tubercle bacilli. When only small amounts of fluid are available, a narrow test tube may be used just wide enough to admit the 10 mm. loop.

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Notes and News

W. K. Kellogg Foundation for Cancer Research.—This foundation has been created by W. K. Kellogg of Battle Creek, Mich., and Pomona, Calif. The foundation will collaborate with the College of Medical Evangelists in cancer and other research work. The sum of approximately $100,000 will be available for the first year, and further provision will be made as the work goes forward.

Josiah Macy Junior Foundation.—This foundation has been established through a gift of $5,000,000 by Mrs. Walter Graeme Ladd, and Ludwig Kast, professor of clinical medicine in the New York Post-Graduate Medical School, has been elected president. The purpose of the foundation is indicated by the following statement in a letter from Mrs. Ladd: "It is my desire that the foundation in the use of this gift should concentrate on a few problems rather than support many undertakings, and that it should primarily devote its interest to fundamental aspects of health, of sickness and of methods for the relief of suffering. To these ends the foundation might give preference in the use of this fund to integrating functions in medical sciences and medical education, for which there seems to be particular need in our age of specialization and technical complexities."

National Institute of Health.—Congress has created a new institution by this name to take the place of the Hygienic Laboratory of the U. S. Public Health Service. An appropriation of $750,000 has been made for new building projects, and the government has been authorized to accept donations by private persons toward the further development of the institute. Fellowships are to be provided for individual investigators who may wish to work in the new institute without permanent appointment in the Public Health Service.

John Phillips Memorial Prize.—The American College of Physicians announces the John Phillips Memorial Prize of $1,500 for meritorious work in internal medicine or contributory sciences. The work must have been done in whole or in part in the United States or Canada. The thesis must be in the English language, and typewritten or printed copies in triplicate must be mailed to E. R. Loveland, executive secretary, 133 South 36th Street, Philadelphia, on or before Aug. 31, 1930.

Grunow Foundation.—It is reported that William C. Grunow, Chicago, has donated $1,000,000 to create the Lois Grunow Memorial Foundation for the furtherance of medical science, and that it is planned to establish laboratories at Phoenix, Ariz.

Medical Fellowship Board of National Research Council.—The next meeting of this board will be held on Oct. 14, 1930. Applications for consideration at this meeting must be in the hands of the secretary of the board (B and 21st Streets, Washington, D. C.) before September first next.

Charles Nicolle, director of the Pasteur Institute of Tunis, and well known for his work on typhus fever for which he was awarded a Nobel Prize in 1928, has been elected a member of the French Academy of Sciences.

At the recent meeting in Atlantic City of the Association of American Physicians, the Kober Medal was awarded to James B. Herrick, Chicago, for his investigations in clinical medicine.

George R. Minot, Boston, has been awarded a gold medal by the National Institute of Social Sciences, New York.

The Trudeau Medal of the National Tuberculosis Association has been awarded to Henry Sewall, Denver, in recognition of his work on tuberculosis.

H. J. B. Fry, pathologist to the Research Institute, Cancer Hospital, London, died on May 5, 1930, from streptococcal infection contracted while making a postmortem examination.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EXPERIMENTAL OBSTRUCTIVE CIRRHOSIS. H. E. MACMAHON, JOHN S. LAWRENCE and S. J. MADDOCK, Am. J. Path. **5**:631, 1929.

Obstructive cirrhosis may be defined as a characteristic form of cirrhosis uniformly limited to all the portal areas throughout the liver. It is caused by an obstruction to the outflow of bile. In the early stages, bile stasis, necrosis and regeneration of individual liver cells, edema and infiltration of the portal areas are the most prominent features. Later there is an apparent increase in the number of bile ducts, the portal connective tissue is increased and with enlargement of the portal areas the liver becomes divided into small, separate and distinct lobules. In the guinea-pig and rabbit, large and small areas of necrosis are early and constant observations. Evidence is presented to show that the proliferation of bile duct epithelium results merely in an apparent increase in the number of bile ducts in the portal area and not in an absolute increase as has been described previously. The proliferation of fibroblasts in the portal areas is interpreted on a mechanical rather than a toxic basis. The origin of the areas of necrosis is discussed, and the opinion is expressed that they are simply areas of infarction. Their relative frequency in lower mammals may be explained on an anatomic and physiologic basis.

AUTHORS' SUMMARY.

THE RATE OF GLYCOLYSIS IN ERYTHREMIA (POLYCYTHEMIA VERA). J. E. COOK and MICHAEL SOMOGYI, Arch. Int. Med. **44**:813, 1929.

The blood of patients with erythremia shows a greatly increased rate of glycolysis. This increased rate is independent of the red cell count as influenced by phenylhydrazine, and shows no direct relation to the proportion of young red cells, when the reticulated count is used as an index of such cells. The increased rate of glycolysis in the usual case of erythremia is not dependent on the increased white count since the increased rate is also present with a low white cell count.

AUTHORS' SUMMARY.

THE TREATMENT OF PNEUMONIA BY INHALATION OF CARBON DIOXIDE. YANDELL HENDERSON, HOWARD W. HAGGARD, POL N. CORYLLOS and GEORGE L. BIRNBAUM, Arch. Int. Med. **45**:72, 1930.

As the background for this study, the following facts are cited: If the lungs are not fully distended soon after birth, pneumonia is likely to develop. After surgical operations, massive, lobar or lobular atelectasis of the lung is a rather frequent occurrence, and is the condition from which postoperative pneumonia develops. This atelectasis or, better, apneumatosis is prevented and relieved, and the risk of pneumonia is eliminated, by the inhalation of carbon dioxide. The inhalation of 5 per cent carbon dioxide in oxygen, which is now the standard treatment for carbon monoxide asphyxia, is also an effective preventive of post-asphyxial pneumonia. In pneumonia it is the blocking of the lung airways, bronchi or bronchioli, by plugs of thick and sticky secretion which is the critical morbidic factor producing atelectasis and the conditions characteristic of an undrained infection. The experiments reported demonstrate these facts: Atelectasis that is induced experimentally in dogs by blocking a bronchus is quickly cleared up and the lung is redistended by the deep breathing induced by inhalation of carbon dioxide in proper dilution. Pneumonia that is induced in dogs by insufflation of a virulent culture of pneumococci is generally overcome, the lung is redistended and the animal is restored to health by inhalation of carbon dioxide sufficient to cause

deep breathing and continued until the pneumonic area is cleared. Success with this therapy for the relief of pneumonia in patients depends on administering the inhalation as early as possible. If medical pneumonia is thus treated early enough, it appears probable that the results may be as effective as those already attained in postoperative and postasphyxial pneumonia.

AUTHORS' SUMMARY.

THE EFFECT OF LESSENED RESPIRATORY RESERVE ON THE BLOOD AND ON THE CIRCULATION. WILLIS S. LEMON, Arch. Int. Med. **45**:115, 1930.

In this study of the respiratory reserve, the muscles ordinarily responsible for the production of inspiration and expiration have been rendered functionless in whole or in part by evulsion of their motor nerve trunks. All of the several functions of the diaphragm have been interfered with so that a state characteristic of a mammal has been changed, and the final state is one that, in respect to the diaphragm, virtually is characteristic more of birds than of mammals. Vital capacity has been lessened, but never beyond the point where it failed to be equivalent to tidal air. The ventilation in liters of air breathed each minute reached a high normal amount but was not distinctly abnormal at any time. The hemoglobin decreased from high to low normal percentages, but the amount of hemoglobin for each hundred cubic centimeters of blood was within normal limits. The hematocrit percentages varied slightly but were never abnormal. The arterial and the venous oxygen content and the oxygen of the blood were essentially normal. However, the oxygen saturation of both arterial and venous blood was lowered. The number of erythrocytes failed to indicate either temporary or permanent erythrocytosis such as might have been anticipated had respiratory competence been destroyed.

The heart has remained normal functionally and has not shown evidence of hypertrophy, and the electrocardiogram cannot be interpreted as evidence to indicate any definite failure of the right ventricle. The experiment illustrates the degree to which muscular dysfunction may be carried before respiratory incompetence develops in an animal that has a normal heart and lungs. It seems to confirm the independence of two fundamental functions having interrelated duties; great loss of reserve in one is required before demonstrable evidence of cooperative support is provided by the other.

AUTHOR'S SUMMARY.

THE PERIPHERAL SURFACE TEMPERATURE IN ARTHRITIS. LILLIE M. WRIGHT and RALPH PEMBERTON, Arch. Int. Med. **45**:147, 1930.

The observations recorded reveal that, under adequately controlled conditions of study, 75 per cent of arthritic subjects maintain at the periphery (the base of the nail), a temperature lower than that of normal persons under comparable circumstances. They also show that under conditions of exposure to cold, the temperature of the arthritic subject at the periphery drops less than does that of normal subjects, partly, but not wholly, because of starting at a lower level. The return of the peripheral temperature of the arthritic subject to the precold room level appears to be relatively slower than that of normal subjects. It is difficult to explain these differences between arthritic and normal subjects on a basis other than that of diminution in, or at least disturbance of, the capillary blood flow. These observations, further, throw light on the mechanism operative in the exacerbations experienced by arthritic subjects during fluctuations in the weather. They imply that the capillary bed and presumably its control by the vasomotor system are less labile in respect to adaptations demanded of it by changes in the environment. Inadequacy of response of this nature doubtless expresses itself in terms of further disturbances in the physiology of the part concerned. In the already handicapped tissues of the arthritic subject, this may mean added dysfunction and pain. Finally, these observations lend further support to the evidence already advanced that an important part of the phenomena of arthritis and the rheumatoid syndrome is referable to disturbances in the peripheral blood flow.

AUTHORS' SUMMARY.

DISTRIBUTION OF THE BLOOD IN SHOCK. A. BLALOCK and H. BRADBURN, Arch. Surg. **20**:26, 1930.

In a series of experiments designed to determine the effects of hemorrhage, injection of histamine, trauma to the intestines, trauma to the brain and trauma to muscular tissue on the oxygen content of the blood, the authors find that after trauma to the intestines or to an extremity, the blood from the portal vein and from the femoral vein each has a higher oxygen content than blood taken from the jugular vessel or renal vein, and the vein from the extremity opposite that which was damaged. The control experiments demonstrated that the oxygen content of the renal vein is higher than that from the right side of the heart or from the portal vein. Both of the latter were of about the same concentration. The blood from the femoral vein was slightly lower than that from the heart, and that from the jugular vein was slightly higher. After hemorrhage and after the injection of histamine, and after traumatizing the brain, the relative values of the oxygen content of the blood taken from these various vessels was the same as in the control experiments. The authors feel that these experiments contradict the theory that the condition of shock is due to a reduction of the oxygen supply and are evidence against the action of a histamine-like substance that produces a general bodily effect. The experiments were all done on dogs under barbital anesthesia, with blood pressure control. The interesting data to be noted in their charts are the averages of the determinations. After hemorrhage, the average oxygen content of all of the blood vessels was considerably lower than that of the control. After the injection of histamine it was only slightly lower, and still somewhat lower after trauma of the brain, and after trauma of the leg, so that while the relative values show very little effect, it would seem that further work would have to be done on the effect of the total reduction of the volumes of oxygen circulating in the blood.

N. ENZER.

ADIPOSOGENITAL DYSTROPHY WITH RETINITIS, MENTAL DEFECT AND POLYDACTYLISM (LAURENCE-MOON-BIEDL SYNDROME). H. LISSER, Endocrinology **13**:533, 1930.

An instance of this rare condition is described clinically in a girl 8 years old.

THE EFFECT OF AN EXCLUSIVE MEAT DIET LASTING ONE YEAR ON THE CARBOHYDRATE TOLERANCE OF TWO NORMAL MEN. E. TOLSTOI, J. Biol. Chem. **83**:747, 1929.

The mechanism for the utilization of carbohydrate may require daily stimulation for normal function. Two men, maintained for a period of one year on a carbohydrate-free diet, manifested a definite diminution in their tolerance for dextrose, which disappeared after the induction of a more normal diet.

ARTHUR LOCKE.

COLLOIDS AS REGULATORS OF THE DIVISION ENERGY OF CELLS. G. L. ROHDENBURG, J. Cancer Research **13**:242, 1929.

Colloids of various kinds (aqueous suspensions of lecithin, cholesterol, egg albumin and gelatin) inhibit the division energy of paramoecia to a varying degree when added to hay infusion.

B. M. FRIED.

IS THE LOCAL VASODILATATION AFTER DIFFERENT TISSUE INJURIES REFERABLE TO A SINGLE CAUSE? PEYTON ROUS and H. P. GILDING, J. Exper. Med. **51**:27, 1930.

Experiment shows that the vascular contraction responsible for Bier's spotting prevails over the local vasodilatation due to mechanical injury of the skin, and

causes the local reddening to blanch. It is without effect, however, on the local vasodilatation caused by histamine pricked into the skin. The results raise doubts concerning the validity of the hypothesis referring all local vasodilatations to the action of a single chemical substance or set of substances ("H substance") liberated within the tissue.

AUTHORS' SUMMARY.

THE EFFECT OF UNILATERAL NEPHRECTOMY ON THE SENILE ATROPHY OF THE KIDNEY IN THE WHITE RAT. ROBERT A. MOORE and LOUIS M. HELLMAN, J. Exper. Med. **51**:51, 1930.

In senility in the white rat there is a decrease in the total number of glomerular units. The decrease in glomerular units is associated with an increase in the average diameter and a greater variation in size of the remaining glomeruli. Unilateral nephrectomy during adult life has no effect on these senile changes.

AUTHORS' SUMMARY.

A COMPARISON OF THE METHOD OF EXCRETION OF NEUTRAL RED AND PHENOL RED BY THE MAMMALIAN KIDNEY. EATON MACKAY and JEAN OLIVER, J. Exper. Med. **51**:161, 1930.

The manner of excretion of phenol red and urea by the frog's kidney differs from that of neutral red. The elimination of the former is by the glomeruli and that of the latter by the tubules. There is a similar difference in the manner of excretion of these substances by the mammalian kidney. It is inferred that this is due to a similar difference in the method of elimination—that in mammals, too, phenol red is eliminated chiefly through the glomeruli and neutral red through the tubules.

AUTHORS' SUMMARY.

EXPERIMENTS RELATING TO A VARIETY OF RAYNAUD'S DISEASE. THOMAS LEWIS, Heart **15**:7, 1929.

The type of Raynaud's disease described is that in which the digits become periodically pale or cyanotic and, after several or many winters of repeated attacks, terminal portions of the digits may be lost by a process of slow dry gangrene. In mild cases recovery may be complete, while in more severe ones the circulation is persistently reduced to a low point at ordinary room temperatures. The fingers remain at the temperature of the surrounding air under all ordinary conditions. The immediate cause of the defective circulation is shown to be spasm of the digital arteries, the venous and capillary vessels not being involved. The spasm is profoundly influenced by temperature, in response to which the vessels behave abnormally. The abnormal element is apparently due to a peculiar condition of the vessel wall locally; it is not the result of a reflex through the vasomotor nerves.

PEARL ZEEK.

MEASURE OF EXPERIMENTAL PULMONARY COLLAPSE. L. BLAVIER, Arch. internat. de méd. expér. **5**:269, 1929.

The effects of a phrenicotomy on the pleural cavity of the same and opposite sides were studied in animals. In these experiments, thin rubber balloons were placed in the pleural cavities at different levels and each one was connected to a water manometer. Readings were taken before and after phrenicotomy. It was found that section of the phrenic nerve leads to a total diminution of variations of pressure in the pleural cavity. The diminution is most marked at the same apex, a little less marked at the same base and opposite apex and scarcely noticeable at the opposite base. It is suggested that the results of the phrenicotomy may extend to the opposite side through inflexion of the mediastinum.

J. N. PATTERSON.

THE REACTIONS OF LEUKOCYTES IN THE EYE. W. JAHNKE, Arch. f. Ophth. **123**: 70, 1929.

Experiments on medium-sized dogs were made to study the leukocyte reaction in the eye to parenteral stimuli as compared with that in the peripheral blood. These reactions were always analogous and different from the reactions in the visceral region. The blood vessels of the eye undergo a change in tonus after the administration of atropine, pilocarpine, epinephrine and cocaine, being constricted after the use of cocaine and dilated after the use of pilocarpine. But the leukocyte count in the eye is not affected by these drugs, whether constricted or dilated vessels result from their administration, and still corresponds to that in the skin. Such pharmacodynamic drugs affect the physiologic relation between caliber of vessel and leukocytosis, as occurs in physiologic reactions, for instance, in active hyperemia. Active hyperemia induced by the local application of heat produces leukocytosis on the one hand and a dilatation of the vessels on the other. The latter causes an increased passage of blood, in contrast to the leukocytosis that results from the parenteral introduction of protein which shows relatively low leukocyte values. The injection of milk did not disturb the equilibrium of leukocytes in the eye and the skin.

CHARLES WEISS.

TRANSPLANTATION OF DRIED OVARY. ALEXANDER LIPSCHÜTZ, Virchows Arch. f. path. Anat. **272**:245, 1929.

Fresh ovary can be transplanted into the kidney of the guinea-pig with from 80 to 100 per cent positive results. Castrated males are used. They show swelling of the mammary glands after two weeks generally. In two out of eight experiments with partly dried ovary swelling of the breast took place, with secretion of milk in one. This ovary had lost 56 per cent of its weight (67 per cent of its water content) by the drying process. In five experiments with ovaries from newborn or very young guinea-pigs, three were positive (loss of weight 52, 56 and 56 per cent). The effect on the nipples was visible only after several weeks. This long incubation period proves that hormones are formed in the transplanted dried ovary. If the drying is made more complete, the effect does not take place. Even after little drying the primordial follicles shrink and their nuclei become pyknotic. It is doubtful whether such damaged follicles become active again or if the hormonic effect comes from a few primordial follicles that have escaped the injuries of drying.

ALFRED PLAUT.

EXPERIMENTAL TRANSPLANTATION OF UTERINE MUCOSA. H. O. NEUMANN, Virchows Arch. f. path. Anat. **272**:265, 1929.

Endometrium of the rabbit transplanted into the peritoneum of the same animal or an animal from the same litter forms cysts when ovarian hormones are present. When castration has been done a few weeks before operation, no cysts are formed and the transplants are resorbed. Transplantation into males is unsuccessful. Such experiments cannot be used as proof for Sampson's theory.

ALFRED PLAUT.

THYROID GLAND AND THYMUS GLAND IN EXPERIMENTAL HYPERTHYROIDISM. E. KLIWANSKAJA-KROLL, Virchows Arch. f. path. Anat. **272**:430, 1929.

Using Hammar's quantitative method, the author has found a definite hypertrophy of the thymus gland in hyperthyroidism of white rats. The animals were fed with dry thyroid gland. The cortex hypertrophies more than the marrow; the Hassal bodies increase in number. As early as ten days after the first thyroid feeding, the increase of thymus substance is noticeable. The normal changes of thymus, which go parallel with age, remain.

ALFRED PLAUT.

Pathologic Anatomy

TUMORS OF THE BRAIN AMONG FILIPINOS. C. REYES, Arch. Neurol. & Psychiat. **22**:1217, 1929.

Of 13,168 autopsies performed at the city morgue of Manila, P. I., from Aug. 1, 1907, to Dec. 31, 1927, the brains were examined in 4,602 (3,081 from males and 1,521 from females). Sixteen tumors were found in the males (0.52 per cent) and twelve in the females (0.79 per cent), a total of twenty-eight tumors, or 0.61 per cent. The presence of tumor was diagnosed or suspected in four, or 18 per cent, of the patients, and in 64 per cent some cerebral symptoms were present which were diagnosed as tuberculous meningitis, cerebral hemorrhage, cerebral embolism, meningism, meningo-encephalitis and in two cases uremia. Modern exploratory methods of diagnosis (ventriculopneumography or even the systematic taking of roentgenograms) were not used. Primary intracranial tumors were found to be more frequent during the second and third decades among females, and during the fourth decade among males; they were generally more frequent among females. Sixty-one per cent were supratentorial, 32 per cent were pituitary and 7 per cent were infratentorial. Forty-seven per cent were gliomas and 33 per cent endotheliomas. Twenty-three per cent of patients with available histories showed no evidence of intracranial tumor and died of acute conditions, the discovery of the tumors having been accidental and unexpected.

G. B. HASSIN.

THE CELLS IN THE EXUDATE OF LEPTOMENINGITIS. THEODORE T. STONE, Arch. Neurol. & Psychiat. **23**:106, 1930.

Stone studied twelve cases of meningitis (purulent, tuberculous, cerebrospinal and syphilitic) to ascertain the origin of some of the meningeal cellular elements, especially the macrophages, in early cases of leptomeningitis. The meninges from the convexity of the brain, from its base and from the pial septum were utilized after the tissues had been fixed in 10 per cent commercial formaldehyde. Various nuclear staining methods and, in addition, osmic acid and silver nitrate were used. Especial attention was paid in these studies to the condition of the pia and the arachnoid. In epidemic meningococcus and septic types of meningitis, the cells of the arachnoid participate in the formation of macrophages; none was seen in the tuberculous and syphilitic forms. The arachnoid cells become large, the nucleus becomes eccentric and the cells become detached and engulf various débris of cell bodies, fat globules, micro-organisms, etc.

G. B. HASSIN.

PARAPLEGIA IN FLEXION: WITH SUBACUTE, COMBINED DEGENERATION OF THE CORD. GEORGE W. HALL and EDWIN F. HIRSCH, Arch. Neurol. & Psychiat. **23**:257, 1930.

Paraplegia in flexion has been described in a number of lesions of the spinal cord (tumors, Pott's disease, multiple sclerosis) and the brain. In the case of Hall and Hirsch the paraplegia was due to subacute, combined degeneration of the cord; it was the second case to be recorded in the literature (the first was reported by H. de Jong in *Acta psychiat. de neurol.* **2**:105, 1927). The patient, a woman, aged 51, showed the first sign (paresthesia) of involvement of the cord one year prior to her admission to the hospital. The paresthesia grew worse, and after a lumbar puncture a paraplegia in flexion of the lower extremities set in. The laboratory examination made at this time revealed a blood picture typical of pernicious anemia, with an absence of free hydrochloric acid and a total acidity of 60 degrees. When the patient was examined after the onset of the paraplegia, she exhibited lively tendon reflexes, with a positive Babinski and similar signs bilaterally, a diminution of epicritic sensibility especially over the lower extremities, where the sense of position was lost, and retention of urine. The serologic tests

gave negative results. Six days later, incontinence of the bowels and bladder and severe pains in the legs developed, which steadily grew worse. The patient developed fever, became delirious and died (six weeks after she had entered the hospital).

Necropsy revealed hypostatic pneumonia, slight bronchopneumonia and practically no gross changes in the brain or the spinal cord. Microscopic examination of the various portions of the brain (stained with hematoxylin and eosin and phosphotungstic acid-hematoxylin; the peduncles were stained with Pal-Weigert method) did not show changes, while that of the spinal cord (the additional staining method used here was that of Bielschowsky) showed degeneration of various tracts in the posterior and lateral columns, such as is commonly described in subacute, combined degeneration of the cord. Numerous vacuolated "foam" cells (gitter cells) were aggregated around the capillaries and small blood vessels. The anterior columns showed but slight degeneration of the nerve fibers.

G. B. HASSIN.

MYASTHENIA GRAVIS WITH STATUS LYMPHATICUS AND MULTIPLE THYMIC GRANULOMAS. NICHOLAS M. ALTER and MICHAEL OSNATO, Arch. Neurol. & Psychiat. **23**:345, 1930.

Alter and Osnato's case of myasthenia gravis was associated with status lymphaticus. A careful pathologic study revealed no changes in the central or peripheral nervous system, but these were abundantly present in the striated muscles. The muscle fibers were surrounded by "lymphoid infiltrations"; many of the fibers were atrophied, showed striation and stained badly. A conspicuous feature was the involvement of the thymus, in which two nodules were present and which showed signs of an extinct and active inflammation. This resulted in involutional fibrosis. The left lobe of the thyroid, which was enlarged and inflamed, contained a large parathyroid body. The lymph nodes, the heart and the aorta were small. There was hypoplasia of the ovaries and of the chromaffin substance of the suprarenals, with atrophy and fibrosis of the hypophysis. There is strong evidence, according to the authors, that the mediastinal nodules may be responsible for the widespread distribution of lymphoid tissue (in the muscles). Early removal of such nodules, which are usually single, may prevent further absorption.

G. B. HASSIN.

PRIMARY INTRAMUSCULAR HEMANGIOMA OF STRIATED MUSCLE. J. S. DAVIS and E. A. KITLOWSKI, Arch. Surg. **20**:39, 1930.

The authors add 11 cases of this tumor, and tabulate 212 cases reported in the literature. They give an extensive clinical review and a discussion of the etiology, pathology, differential diagnosis and treatment. Analysis of the 212 cases shows that the tumor is more frequent in the muscles of the extremities, and that the tumor may present symptoms in the first and second decades, but may not enlarge for many years. However, the analysis shows that the tumor is much more prominent in early life, chiefly occurring before the age of 20. It is equally common in both sexes. Trauma does not seem to be an etiologic factor. The tumors may become very large, since they invade the surrounding muscle, and their early excision is the treatment of choice.

N. ENZER.

THE PATHOGENESIS OF GLOMERULAR NEPHRITIS. WARFIELD T. LONGCOPE, Bull. Johns Hopkins Hosp. **45**:335, 1929.

In conclusion, then, one may summarize the information that can be obtained about primary glomerular nephritis as follows. The disease occurs in two forms —the focal form and the diffuse form. The focal form occurs during acute infections, and in the embolic type is usually ascribed to the deposition of bacteria

in the capillary loops of the glomeruli, where they lead to a necrosis, or to an inflammatory reaction. The diffuse form follows acute infection, proved to be due in such a large proportion of instances to hemolytic streptococci, that for the present it is justifiable to consider at least one variety of acute glomerular nephritis as a manifestation of streptococcic infection. In view of the great frequency of acute streptococcic infection, it must be considered as a rare manifestation. It cannot be proved that acute glomerular nephritis depends on infection by a particular form of streptococcus, or on the invasion of the blood or the involvement of the kidney by streptococci. There is some evidence, however, which indicates that patients suffering from acute nephritis are abnormally susceptible to the products of the growth of hemolytic streptococci and it seems possible that some altered reaction of the tissue, such as occurs in allergy, or some unusual antibody response to the infection is the determining factor in the development of acute glomerular nephritis in individual cases. Permanent recovery is apparently more common in children than in adults. We have no observations to explain the difference. In a small number of adults we have found that recovery has followed elimination of the infection and the infecting organism, while progression of the disease has been coincidental with the persistence or the recurrence of hemolytic streptococcus infections. It further appears evident that there are instances of Bright's disease that run their entire course as progressive or recurrent diffuse inflammatory glomerulitis, without involvement of the renal arteries or arterioles, and with changes in the renal tubules that may be regarded as secondary to the glomerular lesion and to the diffuse inflammatory reaction of the interstitial tissue. As a working hypothesis, therefore, we would suggest that it may be possible to differentiate, as one form of Bright's disease, a primary and specific glomerular nephritis which is to be interpreted probably as a manifestation of streptococcus infections in persons who may be allergic to the streptococcus or its products of growth, or who possess some other peculiar form of tissue response to a local streptococcic infection.

AUTHOR'S SUMMARY.

PARATHYREOPRIAL TETANY LASTING ONE YEAR, NECROPSY. H. LISSER and H. C. SHEPARDSON, Endocrinology **13**:427, 1929.

On removal of a goiter, tetany developed. The patient was a woman, aged 30. Under treatment with parathyroid extract, which gradually lost its effect, life was maintained for one year when death occurred from acute sepsis. Three parathyroid bodies were found in the goiter after its removal, and autopsy failed to disclose any parathyroid tissue. There was no evidence of secondary disturbances in other ductless glands.

CALCIFICATION IN PITUITARY ADENOMAS. E. M. DEERY, Endocrinology **13**:455, 1929.

In roentgenograms of nineteen adenomas of all types, areas of calcification were indicated by shadows within the growth, but calcification was not detected at necropsy or in microscopic sections of bits of tissue. No opportunity was given to examine the entire growth for calcification in any of these cases. In an instance studied since the report went to press, calcification was found on microscopic examination.

HYPERPLASIA OF THE FEMALE GENITAL TRACT IN ACROMEGALY. H. M. TEEL, Endocrinology **13**:521, 1929.

In a woman, aged 49, with advancing acromegaly for seven years, the entire genital tract was markedly hyperplastic, especially the uterus. It is assumed that this overgrowth was the effect of an eosinophilic pituitary adenoma and consequently in nature was similar to the genital hyperplasia inducible in dogs by alkaline extracts of the anterior lobe of the hypophysis.

PITUITARY ADENOMA WITH GYNECOMASTIA. R. C. MOEHLIG, Endocrinology **13**:529, 1929.

The patient was 52 years of age. Impotence, feminine distribution of pubic hair and gynecomastia gradually developed with evidences of a large pituitary growth which post mortem was found to be a chromophobe adenoma.

PRESSURE ATROPHY OF THE BRAIN. TEMPLE FAY, J. A. M. A. **94**:245, 1930.

By encephalography it has been determined that an extensive atrophy of the brain may follow relatively slight injury. The atrophy affects preferably the frontal and parietal areas of the cortex and is regarded as due to pressure from increase in the arachnoid fluid owing to obstruction in its circulation.

STUDIES ON INFLAMMATION. VALY MENKIN and MIRIAM F. MENKIN, J. Exper. Med. **51**:285, 1930.

By means of a colorimetric method, the concentration of trypan blue in capillaries can be estimated by direct observation and its changes followed as the dye passes out of the circulating blood stream. The change in concentration of trypan blue in the capillaries of both the normal and the inflamed mesentery of frogs can be described by two separate exponential equations of the type: $y = be^{-ax}$. From these equations, it is found that the rate of fall of concentration following intraventricular injection of the dye is almost twice as great in the capillaries of the inflamed as in those of the normal mesentery. This difference is a measure of increased permeability with inflammation.

AUTHORS' SUMMARY.

TUMORS OF THE CAROTID BODY. A. D. BEVAN and E. R. MCCARTHY, Surg. Gynec. Obst. **49**:764, 1929.

A brownish, red purple, walnut sized tumor was revealed, by exploratory operation, at the junction of the common, external and internal carotid arteries. The tumor was not removed because of the extensive vascular resection necessary in these cases. The reports of 133 cases is reviewed.

RICHARD A. LIFVENDAHL.

THE RELATION OF MATERNAL PELVIC DISEASE TO DEFORMITIES IN THE NEWBORN. L. GOLDSTEIN and D. P. MURPHY, Surg. Gynec. Obst. **49**:804, 1929.

Three of 310 children born of women suffering from idiopathic uterine hemorrhage, myoma, adnexitis, amenorrhea or carcinoma of the cervix or vulva were deformed. The abnormalities included anencephaly, microcephaly and hydrocephaly. This incidence of gross deformities corresponds to the birth rate of malformed children in the general population, indicating, that the presence of uterine or adnexal pathologic process has no relation to the production of deformities in new-born children.

RICHARD A. LIFVENDAHL.

PRIMARY CARCINOMA OF THE URETER. L. M. ROUSSELOT and J. D. LAMON, Surg. Gynec. Obst. **50**:17, 1930.

In the upper part of the right ureter was a squamous cell carcinoma. In reviewing the forty-nine recorded cases it was found that these growths usually are of the papillary type and spread usually by way of the lymphatic or venous channels. In this case there were metastatic growths in the regional and bronchial lymph nodes, suprarenals, pancreas, liver, lungs and pleura. Although calculi, as a rule, are not associated with ureteral carcinoma, calculi were present in the corresponding kidney.

RICHARD A. LIFVENDAHL.

RIGHT PARADUODENAL HERNIA AND ISOLATED HYPERPLASTIC TUBERCULOUS OBSTRUCTION. J. C. MASSON and A. H. MCINDOE, Surg. Gynec. Obst. **50**:29, 1930.

Thirty-four cases of right paraduodenal hernia have been described. In the case reported, an oval hernial opening 10 cm. long was present to the left of the superior mesenteric artery, in the left lumbar region, having its long axis in the direction of the mesentery. The mesenteric artery was kinked over the edge and extended into the hernial sac, which extended 22.5 cm. caudad and slightly to the left and was located behind the posterior parietal peritoneum. Three fourths of the small intestine was found in this outpouching, and the proximal jejunum was markedly dilated and hypertrophied as the result of a firm tuberculous fibrous constricting ring located 120 cm. proximal to the ileocecal valve. Calcified tuberculous lymph glands were found in the regional mesenteric lymph glands. A discussion of the other types of this hernia and intestinal tuberculosis is given.

RICHARD A. LIFVENDAHL.

THE EFFECT OF CHOLECYSTENTEROSTOMY ON THE BILIARY TRACT. GATEWOOD and S. E. LAWTON, Surg. Gynec. Obst. **50**:40, 1930.

Cholecystgastrostomy on dogs showed thickened gallbladders, round cell infiltration of the vesical mucosa, in a few of the common ducts and in the periportal areas of the liver. Acute and chronic retrogressive changes were noted in the centers of the liver lobules. *B. coli* and *Proteus vulgaris* were cultured from the gallbladder and the common duct but no bacterial growth was obtained from the liver. In man, however, from the small amount of data available, these changes have been rarely recorded.

RICHARD A. LIFVENDAHL.

TWO CASES OF MYELOMATOSIS. D. F. CAPPELL, J. Path. & Bact. **32**:293, 1929.

One case of myelomatosis was of a diffuse character, involving the marrow of the ribs uniformly and the femur in its upper third in irregular nodules. There were multiple, unhealed fractures of the ribs and a collapse of the sixth thoracic and fourth lumbar vertebrae. Plasma cells, often containing mitoses, dominated the picture in histologic preparations of the marrow, liver and spleen, although myeloblasts and transition forms were seen. In the second case, nodules were encountered in the ribs, femur and periportal spaces of the liver. Mononuclear and reticulated cells, in addition to plasma cells, were abundant in this case. There were many mononuclear cells in the pneumonic exudate.

GEORGE RUKSTINAT.

INTRAVITAM STAINING. D. F. CAPPELL, J. Path. & Bact. **32**:595, 1929.

Three main classes of intravitam stains were employed: those rapidly absorbed, as trypan blue, vital red and lithium carbonate; those slowly absorbed, as isamine blue, diaminefast scarlet acid, and insoluble suspensoid preparations, as india ink and saccharated oxide of iron. It was concluded that intravitam and supravital staining of cells (apart from mitochondria) was due to the concentration of dye within vacuoles and granules in the cells—the "segregation apparatus." The appearance of dye in the cells was not regarded as a simple precipitation but as an active binding which varied with the functional activity of the cells. It was found that, contrary to the popular belief, the soluble dyes were demonstrable in the plasma several days after intravenous injection. Because of this fact it is necessary to wait until the dye has disappeared from the plasma before starting experiments involving intravitam-stained cells and pathologic processes; otherwise, previously unstained cells and emigrated cells or proliferated cells called forth by the pathologic stimulus might be stained and lead to false conclusions. Results from experiments with intravitam and supravital stains on all body tissues are recorded.

GEORGE RUKSTINAT.

A Case of Periarteritis Nodosa. J. Gray, J. Path. & Bact. **32**:787, 1929.

A case of periarteritis nodosa is reported in a woman, aged 21, who died after decapsulation of the kidney. Lesions were abundant in the coronary and renal arteries and branches of the hepatic. An interesting feature was the occurrence of plasma cells and particularly eosinophils in great abundancee.

George Rukstinat.

Aschoff Nodule in Rheumatic Pneumonia. A. D. Fraser, Lancet **1**:70, 1930.

A specific form of pneumonia may occur in acute rheumatic fever. In the acute stage the lesion is marked by vascular changes, proliferation and necrosis of alveolar walls, and destruction of bronchi in the areas involved. It resembles acute interstitial pneumonia. Typical Aschoff bodies occur in the interstitial tissue, most prominently in the interlobular septums. A chronic stage may supervene with more or less fibrosis and now the Aschoff nodule appears to be absent.

Echinococcus Cyst of the Heart. C. Bacaloglu and Others, Ann. de méd. **26**:242, 1929.

A case with multiple embolism is described. The emboli had cystic contents.

Stenosis and Occlusion of Internal Uterine Os. Eva Glück, Beitr. z. path. Anat. u. z. allg. Path. **81**:121, 1928.

The relatively frequent occurrence of hydrometra in elderly women, as seen at necropsy, led to a study of the region of the internal os, with the aim of determining the cause of the dilatation of the uterine cavity. In the routine post-mortem examination of 100 successive women over 50 years of age, hydrometra of varying grades was found in half. In most of these the degree of dilatation was only moderate, extreme grades being rare. In only one third of the 100 uteruses examined was the region of the internal os normal; in the remaining two-thirds it revealed varying degrees of change resulting in extreme cases to complete occlusion of the os. The changes that lead to narrowing and obliteration of the internal os were studied by means of serial sections of fifteen uteruses. The earliest change is a loss of the superficial epithelium. This is followed by proliferation of the subepithelial stroma, the newly formed tissue becoming transformed into fibrous scar tissue which narrows or occludes the lumen. The area of such involvement was usually not more than 1 mm. in length. In a few instances the lumen was closed off by two or more transverse fibrous septums. The uterine glands in the involved area may persist. Their openings become occluded by the fibrotic process and they become transformed into cysts, the presence of which may be a factor in the narrowing of the lumen. The process which leads to the changes noted at the internal os is considered senile. The cervical canal was normal in those cases in which the internal os was obliterated. Narrowing of the external os, which was noted in a few cases, was due to chronic inflammatory changes in this region which were not identical with the senile fibrosis at the internal os.

O. T. Schultz.

Hyaline Fibrosis of Brain, Lung and Suprarenals. E. Randerath, Beitr. z. path. Anat. u. z. allg. Path. **81**:145, 1928.

Randerath presents, as a very unusual condition, a case with multiple areas of hyalinized fibrosis in various organs. Histologic observations and discussion of their interpretation are given in detail. The patient was a woman, aged 50, who, seven years before death, had had a prolonged attack of respiratory trouble

termed grip. Progressive weakness of various groups of muscles developed some time before her admission to the hospital, and death was apparently due to bronchopneumonia. The clinical diagnosis was bronchopneumonia and questionable abscess, tuberculosis or embolism of the brain. Necropsy revealed, in addition to terminal bronchopneumonia, marked fibrosis of the left lung, fibrosis of the thyroid and both suprarenals and the presence of multiple grayish, scar-like areas in the cerebral cortex. Microscopically, the left lung, brain, thyroid and suprarenals contained multiple areas of dense fibrous tissue which was markedly hyalinized. In the superficial portion of the cerebral cortex, the blood vessels were surrounded by mantles of lymphocytic infiltration. Both the cortex and the medulla of both suprarenal glands were extensively involved in the hyaline fibrotic process, and lymphocytic infiltration was present in the cortex and in the surrounding adipose tissue. There had been no evidence of Addison's disease during life. The fibrosis of the thyroid was like that of the condition which Wegelin has termed inflammatory sclerosis of the thyroid. In his discussion of the etiology and nature of the process described, Randereth excludes syphilis and adopts the view that the conditions described were the results of a generalized infection of long duration following influenza. This led to the formation of areas of fibrosis in various organs. In such areas, deficient circulation led to destruction of tissue, which in its turn caused the deposition of hyalin through an antigen-antibody reaction, as postulated by Loeschke.

O. T. SCHULTZ.

ARTERIOSCLEROSIS OF THE PULMONARY ARTERY. U. STEINBERG. Beitr. z. path. Anat. u. z. allg. Path. **82**:307, 1929.

Steinberg's discussion of arteriosclerosis of the pulmonary artery is limited to the secondary form of the disease, that form in which some known factor, mechanical, toxic infectious or chemical, may be accepted as having a causative rôle. Discussion of the much rarer primary form, which leads to hypertrophy of the right ventricle, and for which no cause can be assigned, is reserved for a later paper. The present study is based on 500 necropsies of persons whose age ranged from 15 to more than 94 years. Arteriosclerosis of the pulmonary artery is usually nodular, the nodules varying in diameter from a millimeter or two to a centimeter or more. The number of nodular lesions varies from a few to so many that the lesions are almost confluent. Vessels of the third and fourth order, with a circumference of from 2 to 4 cm., are most often involved. More rarely the main trunks are the seat of the process, and the finer vessels are rarely involved. The nodular lesions always contained lipoid substances and were usually associated with elastic tissue hyperplasia and intimal proliferation. In rare instances the process was diffuse rather than nodular. In the statistical study of the material, especial attention was paid to the presence of lesions which might be presumed to cause an increased pressure within the pulmonary circuit. Such processes, to which an important rôle has been ascribed in the causation of pulmonary artery arteriosclerosis, are chronic circulatory disturbances, emphysema, pulmonary fibrosis, pleural thickening, and deformities leading to decrease in the size of the chest cavity. Attention was paid to toxic infectious processes, and the concomitant occurrence of arteriosclerosis of the general circulation received careful consideration. Steinberg concludes that mechanical factors which lead to increased pressure within the pulmonary circuit are less important in the causation of arteriosclerosis of the pulmonary artery than has been held to be the case by most previous observers. The condition is more frequently associated with arteriosclerosis of the general circulation than with any other condition. Steinberg accepts Anitschkow's view that disturbance of lipoid metabolism is the fundamental factor in arteriosclerosis, of the lesser as well as of the general circulation. Given such a disturbance, then mechanical factors play a secondary part in the establishment of the process.

O. T. SCHULTZ.

OSTEITIS FIBROSA. M. WEBER, Beitr. z. path. Anat. u. z. allg. Path. **82**:383; 514, 1929.

The changes noted in the osseous system of an 8½ months old female Boston terrier form the basis of a 172 page discussion of osteitis fibrosa, for which the author prefers the term osteodystrophia fibrosa as a more generally applicable name for a disease of which the condition previously known as osteitis fibrosa is only one type. The upper jaw was deformed by a large tumor-like mass, composed in part of cellular osteoid tissue and ossifying fibroblastic tissue, being in these respects similar to the intra-osseous epulis described by a number of writers in the jaw of lower animals, and made up in part of cystic spaces. In the rest of the skeleton, two kinds of change occurred together. One was an osteoporotic process, which was characterized by the presence of numerous giant cells within the bone, and of spaces from which the bone had been resorbed. The second process was one of hyperplastic bone formation, characterized by the production of osteoid tissue that became fibrotic and partly ossified. This process was associated with fibrosis of the marrow. The points of similarity to and difference from rickets, osteomalacia, and scurvy are discussed in relation to the differential diagnosis of the condition described. Weber accepts Christeller's classification of osteodystrophia fibrosa. The latter writer recognized two main groups of the condition, an osteoporotic form and an osteosclerotic form, the latter being the healed or healing stage of the former. Each of these groups was subdivided into a hyperostotic form and a hypo-ostotic form, depending on whether bone formation or bone resorption is predominant. Any of these forms may be associated with cyst and pseudotumor formation. Juvenile and adult forms are recognized. Taking into account the classification and the changes noted by himself, Weber gives to the condition described the name of juvenile, cyst and pseudotumor forming, hyperostotic-porotic form of osteodystrophia fibrosa. The type with cyst and pseudotumor formation is extremely rare in the dog, although it has been described in a variety of other species of lower animals, as well as in man. A detailed description of the microscopic observations is followed by a general discussion of the process of normal bone formation, to a disturbance of which osteodystrophia fibrosa is ascribed. The phases of bone formation from the undifferentiated mesenchymal ground substance are differentiation, the formation of ossification centers, the formation of cortical bone and resorption of bone. Osteodystrophia fibrosa is looked on as the reaction of the osseous system to a stimulus, the latter possibly a metabolic disturbance. The immediate reaction is resorption of bone. The bone responds by a proliferative reaction which results in the formation of undifferentiated mesenchymal ground substance. From this there is formed by differentiation fibrous tissue and fibrillated bone. Cortical bone is not formed except as osteoid tissue. The cysts and pseudotumors result from abnormal differentiation of undifferentiated mesenchyme, in situations such as the jaw, when mechanical factors, as the act of chewing, play a part. The culmination of the progressive phase of osteodystrophia is reached when all the original cortical bone has been replaced by fibrous bone. The end of the progressive stage and the beginning of healing are manifested in the cessation of resorption and in the reformation of cortical bone. It should be the aim of feeding experiments to bring about a state to which the bone would react by such changes as those that characterize osteodystrophia fibrosa. Feeding experiments designed to bring about a cessation of the process would, if successful, be of the greatest benefit in the therapy of the disease, especially of the human being. The article closes with a bibliography of 228 titles.

O. T. SCHULTZ.

CARTILAGINOUS NODULES OF THE INTERVERTEBRAL DISKS. R. ANDRAE, Beitr. z. path. Anat. u. z. allg. Path. **82**:464, 1929.

In the series of vertebral columns examined, small cartilaginous nodules were found present in the posterior ends of the intervertebral disks in 12 per cent of males and in 19 per cent of females. The nodules are usually multiple, are most

numerous in the thoracic portion of the column, and lie beneath the posterior longitudinal ligament. They may become vascularized or ossified. They seem to be of little significance. The study excites interest chiefly because it was based on the examination of 174 male and 1,949 female vertebral columns and comes from Schmorl's institute, where the right femur is removed routinely at necropsy, and the left femur and the entire vertebral column in most bodies coming to post-mortem examination.

O. T. SCHULTZ.

COMPARATIVE HISTOLOGY OF GASTRIC MUCOSA. H. BILLENKAMP, Beitr. z. path. Anat. u. z. allg. Path. **82**:475, 1929.

Billenkamp made a histologic study of the normal gastric mucosa of fifteen species of mammals representing the following classes: insectivora, rodentia, carnivora, ungulata and primates. He compared the histology of the mucosa of the greater curvature with that of the "Magenstrasse," the region characterized by the four folds which run from the cardia along the lesser curvature to spread out in the pyloric region. It is in this region of the lesser curvature and pylorus that carcinoma, ulcer and epithelial metaplasia occur most frequently in the human stomach. In most of the animals examined, the histologic structure of the region in question differed from that of the greater curvature. In several of the species, no glands of the kind present in the body of the stomach occur in the lesser curvature or pyloric region. In those species in which fundus glands are present in the region studied, they are limited to a short stretch near the cardia. In all species the fundus mucosa extends farther distally along the greater than along the lesser curvature. In a few species, the junction between fundic and pyloric mucosa takes a straight course around the stomach at right angles to the long axis of the stomach. In some species, there is present between the fundic and pyloric types of mucosa an intermediate zone in which the glands contain no chief cells. In most of the species examined, the thickness of the chief cell layer increases progressively from lesser to greater curvature.

O. T. SCHULTZ.

GLYCOGENIC HEPATONEPHROMEGALY. E. VON GIERKE, Beitr. z. path. Anat. u. z. allg. Path. **82**:497, 1929.

Von Gierke presents the case report of a condition which he believes to have no counterpart in the literature. The case is that of a girl who died at the age of 8 years. The family history was negative, and birth and early development had been normal. Unusual prominence of the abdomen had been noted by the family physician at the age of 2 or 3 months and had been present since birth, according to the mother. Throughout its life the child had been susceptible to infections of the upper respiratory tract. She had had a number of attacks of nosebleed, and had been treated for rickets, from which she recovered. The child had been admitted to the hospital when 5 years old. At this time the abdomen was large. The liver was greatly increased in size. There was questionable enlargement of the spleen. There was moderate secondary anemia, with relative lymphocytosis. The suggested clinical diagnosis at this time was Banti's disease. The final admission was for an acute infection of the upper respiratory tract, which resulted in death. At necropsy, the liver weighed 2,000 Gm. instead of 634 Gm. which is the average weight for the age and sex of the patient. The kidney weighed 245 Gm. instead of the average 133 Gm. There was no ascites. The spleen was of normal size and weight. The thymus and suprarenal glands were small. Microscopic examination revealed the presence of moderate amounts of fat in the liver cells. The latter did not give the lipoid reactions of Niemann-Pick disease (lipoid histiocytosis, Bloom). The liver cells were filled with glycogen, as were also the tubular epithelia of the renal cortex. The glycogen could be stained by carmine and gave the iodine reaction. The liver contained 10.43 per cent of glycogen calculated for moist weight of the tissue, and 33.72 per cent calculated for the dry weight. The kidney contained 6.53 per cent glycogen, moist

weight, and 36.82 per cent, dry weight. The glycogen did not disappear from fresh liver tissue kept for six days in the incubator in normal physiologic solution of sodium chloride and chloroform water. The pancreas was histologically normal. After von Gierke had completed the study of his case, he learned of an apparently similar one that had come to necropsy in Vienna in 1928. This case he also presents. The child was a boy, aged 4 years and 10 months. The liver and kidneys were enlarged, and the parenchymatous cells of these organs contained large amounts of glycogen. As a working hypothesis to explain the condition reported, the author postulates a disturbance of intracellular glycogen metabolism, which leads to deposition of the glycogen in the cells of the liver and kidney. Early embryonic tissues, especially liver, kidney and muscle, are rich in glycogen, indicating the early development of the property of intracellular glycogen synthesis. The glycogen store disappears from the tissues at or shortly before birth, indicating a later development of the property of intracellular glycogenolysis. In the condition reported, it is supposed that the cells of the liver and kidney failed to develop the normal property of splitting glycogen.

O. T. SCHULTZ.

HYALINE BODIES IN TESTICLE. C. BLUMENSAAT, Virchows Arch. f. path. Anat. **273**:51, 1929.

In six of fifty-one boys ranging from 1 to 15 years of age, the testicles contained hyaline bodies similar to corpora amylacea, located in the lumen of convoluted tubules. They appeared to originate from desquamated spermatogones. In all six cases death had been caused by a disease located in the skull (three times otitis, extradural abscess, glioma, sarcoma). Lipoid and iron deposits in the testicle show the same preference.

ALFRED PLAUT.

NEUROMA AND CARCINOID OF VERMIFORM APPENDIX. HEINZ BARTH, Virchows Arch. f. path. Anat. **273**:62, 1929.

The histogenesis of carcinoid is obscure. The different theories contradict each other. In a woman, aged 70, the center of the obliterated appendix was occupied by a neuroma, parts of which contained argentaffine cells. The amount of nervous tissue in the wall was large. This coexistence of neuroma and carcinoid is not accidental; there is some connection between the yellow cells of the intestinal mucosa and the nervous apparatus of the intestine. In a girl, aged 19, the appendix had the thickness of a little finger and contained a diffuse, carcinoid-like tumor with metastasis in the ovary. This tumor contained giant cells with vacuoles and granules. The patient is alive twelve years after operation. The presence of metastasis from carcinoid in a lymph node, for instance, generally does not mean an unfavorable prognosis. In a girl, aged 16, an acute inflammation of the appendix was restricted to the portion between a small carcinoid and the tip. On the other hand, a small carcinoid in a girl, aged 10, seemed to be secondary to an acute appendicitis.

ALFRED PLAUT.

CELL CONTENTS AND IRON IN THE SPLEEN OF FETUS AND NEW-BORN. I. E. LEWIN, Virchows Arch. f. path. Anat. **273**:168, 1929.

In eighty-five fetuses and new-born infants the spleens were examined; thirty-five were mature and fifty were premature. The follicles are smaller in the new-born than in the adult; the external zone often is indistinct. Granulocytes are found in different numbers. Eosinophil cells are always present. Basophils are few; they are found only after fixation in absolute alcohol. Their number does not increase with toxic conditions or with congenital syphilis. Plasma cells are absent. No megakaryocytes are found. Immature red cells are found in varying numbers and varying distribution.

In the mature new-born the spleen generally gives a strong iron reaction. It was the same in the spleen of four infants born during the eighth and ninth

month. In the spleen of forty-four immature infants and of four mature infants little or no iron was found (Hueck's iron reaction was used). In the sixth and seventh month iron reaction is negative. Stasis and duration of labor bear no relation to the iron reaction. In two prematurely born infants there were hemorrhages in the spleen, but the iron reaction was negative. These results partly are at variance with those of Lubarsch.

ALFRED PLAUT.

THE HEALING OF JOINT FRACTURES. LEO LÖW-BEER, Virchows Arch. f. path. Anat. **273**:191, 1929.

Few microscopic examinations of joint fractures are reported in the literature; therefore the author gives (in more than fifty pages) a detailed description of six joint fractures from autopsy material. There are twenty-one photographs. The many details must be studied in the original paper with the aid of the photographs. The periosteal callus participates little in the bony consolidation. The final regeneration of bone and marrow is so complete that the site of fracture may become indiscernible even under the microscope. Tendinous callus bridges over the gaping fracture cleft; intercalar bones in it start the bony consolidation. The fracture line in the cartilage remains visible since the fibrocartilage which fills it is more bluish than the old hyaline cartilage. In some instances the cleft remains filled with fibrous tissue which originated from bone-marrow. The occurrence of secondary arthritis depends on dislocation. Small accessory microscopic fractures in the neighborhood are frequent.

ALFRED PLAUT.

ISOLATED TUBERCULOSIS OF MYOCARDIUM. L. BERGER and J. CHARLES MILLER, Virchows Arch. f. path. Anat. **273**:250, 1929.

The heart, which was that of a mentally defective man, aged 57, had six caseous foci from 0.5 to 2 cm. in diameter. The pericardium was partly adherent; the valves and aorta were normal. No gross or microscopic lesions were seen in any other organ. At the edge of the foci was a narrow margin of epithelioid cells and lymphocytes with few atypical giant cells; some of those contained tubercle bacilli. Only two similar cases are reported in the literature.

ALFRED PLAUT.

Pathologic Chemistry and Physics

THE COMPOSITION OF HUMAN SWEAT. RALPH PEMBERTON, F. A. CAJORI and C. Y. CROUTEN, Ann. Int. Med. **2**:1243, 1929.

Under normal conditions sweat may have either an acid or an alkaline reaction, the p_H values ranging from 4.8 to 8.4, which is essentially the range that has been observed for urine. Acid sweats contain very small amounts of carbon dioxide, and this reaction is not effected by boiling or aeration; the acidity appears to depend on some component other than carbon dioxide. Alkaline sweats contain more carbon dioxide. The cause of the acidity of sweat remains undetermined. The change in reaction from acid to alkaline during long-continued sweating appears to be the result of the actual excretion of alkaline substances. The nitrogen and chloride content of the sweat of arthritic patients does not differ appreciably from the values obtained for normal sweat. Normally high nitrogen values were obtained in the sweat of nephritic patients. These observations suggest the possibility that in nephritis the skin may serve as a valuable path for the excretion of nitrogenous substances.

WALTER M. SIMPSON.

PHOSPHORUS IN THE BLOOD AND URINE. IRWIN SCHULZ, Ann. Int. Med. **3**:667, 1930.

The inorganic phosphorus values of the plasma are equal to or less than the values for whole blood in normal, fasting persons. In patients with nephritis

with retention of phosphorus, the level of inorganic phosphorus in the plasma is greater than that in the whole blood. Retention of phosphorus associated with retention of creatinine in patients with chronic nephritis indicates a fatal prognosis. If a nontoxic mixture of solution of acid sodium phosphate, 9 per cent, and of solution of alkaline sodium phosphate, 9.6 per cent, in a ratio of 3 parts of the former to 17 parts of the latter, is injected intravenously into a normal man, it will produce an immediate rise, followed by a gradual fall, in the inorganic phosphorus of the blood. It causes an increase in the amount of inorganic phosphorus excreted in the urine and feces. In the normal, fasting subject, 50 per cent of the injected phosphorus may be recovered from the urine within four hours. In nephritis the amount of phosphorus recovered is decreased as the amount of renal injury is increased. Furthermore, the return of the level of inorganic phosphorus in the blood to that preceding injection is slower in patients with nephritis than in the normal subject.

WALTER M. SIMPSON.

BILIRUBIN IN EFFUSIONS OF THE JOINTS. D. H. KLING, Arch. Surg. **20**:17, 1930.

In traumatic, hemorrhagic effusions of the joints, the fluid has a higher icterus index than the circulating blood, and this icteric index increases as the disintegration of the extravasated red cells increases. In inflammatory effusions, the icteric index is the same or slightly less than that of the blood. In traumatic effusions of the joints accompanied by intra-articular fractures, the bilirubin content of this fluid is still higher, due, the author believes, to the leakage of venous blood from the bone-marrow.

N. ENZER.

VARIATIONS IN THE PLASMA CHOLESTEROL AND CHOLESTEROL ESTHER CONTENT IN HOG CHOLERA. RICHARD E. SHOPE, J. Exper. Med. **51**:179, 1930.

The cholesterol content and cholesterol ester content of the plasma of swine experimentally infected with hog cholera exhibit a regular succession of changes. During the period of incubation of the disease, for three or more days following inoculation with the virus of hog cholera, hypocholesterolemia prevails. This is followed by a period of hypercholesterolemia, which is coincident with the onset of the clinical manifestations of the disease. The hypercholesterolemia after from four to seven days gives way to a second period of hypocholesterolemia, more marked and more prolonged than that observed immediately after inoculation. In the present experiments, this second period lasted eight and eleven days in the two animals surviving long enough for the study of it, and was followed by a second period of hypercholesterolemia. In the one animal surviving this period for eight days, a third period of irregular and fluctuating hypocholesterolemia set in. A comparison with the results in other acute infections indicates that hog cholera is unique in showing alternating periods of hypocholesterolemia and hypercholesterolemia. A normal hog inoculated with *Bacillus suisepticus* rapidly developed the typical marked hypocholesterolemia, whereas an animal infected with hog cholera and then inoculated with *B. suisepticus* failed to show the decrease in the cholesterol content of the plasma.

AUTHOR'S SUMMARY.

ON THE ACTION OF SERUM ON THE FIBRINS OF VARIOUS SPECIES. J. VAN DER SCHEER, J. Immunol. **18**:17, 1930.

The author tried without success to duplicate the experiments by Fuch and von Falkenhausen, from which it would follow that the distinction of proteins (fibrin) of various species and races can be made by means of serum ferments.

AUTHOR'S SUMMARY.

THE COLLOIDAL THEORY OF SILICOSIS. PATRICK HEFFERNAN, Tubercle **11**:61, 1929.

The "colloidal" theory of the action of inhaled silica dust is briefly: the silica particles, crystalline, cryptocrystalline or amorphous, are engulfed by phagocytes in the wall of the alveoli, and conveyed into the lymphatic channels, where they come to an arrest. The silica particle, within the phagocyte, is "hydrated" at its surface into colloidal silica hydrosol, the production of a "soluble" alkaline silicate being a temporary intermediate stage in the process of hydration. The hydration occurs at the expense of the protoplasmic fluid of the phagocyte, which becomes vacuolated and dies, leaving a "ghost" of cell behind. The foregoing processes are retarded if the silica particle has a protective coating, e. g., of carbon, clay, etc., and are accelerated by the presence of alkali, e. g., if the silica particle has a coating of alkaline soap. After the death of the phagocyte, the action spreads to the surrounding cells, which are similarly influenced. So far, the facts are capable of verification, and the net result is destruction of tissue cells and, in due time, replacement. Whether the action is one of simple dehydration of tissue cells or whether certain constituents of the cell protoplasm are selectively absorbed by the silica hydrosol, or whether reactions such as coagulation of cell colloids and the formation of silico-organic compounds, stoichiometric or adsorptive occur, is still unknown. The process may continue until all the silica particle is dissolved, when equilibrium is attained by some such means as the formation of relatively stable silico-organic substances (e. g., cholesterol silicate in bird's feathers) or adsorption compounds; or by the coagulation of the silica hydrosol into an irreversible gel; or by the elimination of the silica, in its "soluble" state, in the urine. On the other hand, the hydration of the silica particle may cease, temporarily or permanently, before the particle is completely "dissolved." In this case there would be a central core of undissolved silica surrounded by silica hydrosol or gel, next to this a zone of the "ghosts" of dead cells, outside of which would be a zone of small cell infiltration or fibrosis. Such a system would constitute a typical "silicotic" nodule. Such a dormant silica nodule next could be reactivated should the protective barrier break down and alkaline tissue juices again come into contact with the silica particle. "Silicotosis" is believed to be a true silicosis, possibly modified by the calcium, iron, magnesion, aluminum, etc., from which the colloidal silica has been set free. The question of the elimination of silica from the body urgently needs investigation.

H. J. CORPER.

PLASMA PROTEINS AND SEDIMENTATION RATE OF RED CELLS. F. REICHE and F. FRETWURST, Beitr. z. Klin. d. Tuberk. **72**:484, 1929.

The fractions of the plasma protein and their relative amounts are not the main factors in determining the sedimentation rate.

MAX PINNER.

OXALATURIA AND INCREASED URINARY EXCRETION OF OXALIC ACID IN TUBERCULOSIS. J. A. LANGER and T. LITTIG, Beitr. z. Klin. d. Tuberk. **72**:492, 1929.

The increased excretion of oxalic acid in tuberculosis is probably related to the catabolism of the fatty acids in the liver and is a manifestation of an impairment of the intermediary metabolism. The microscopic demonstration of oxalates in the urine has no diagnostic significance.

MAX PINNER.

Microbiology and Parasitology

A STUDY OF BACTERIOPHAGE IN TISSUE CULTURES. I. DRESEL and M. R. LEWIS, Am. J. Hyg. **11**: 189, 1930.

The activity of bacteriophage (mouse typhoid phage) on homologus bacteria (mouse typhoid bacilli) was not demonstrated in tissue cultures, either from susceptible or from refractory animals. On the other hand, such tissue cultures

made on agar plates, instead of hanging drop preparations, showed the bacteriophage to be active. The bacteriophage was not influenced by the growth of the cells in tissue cultures, regardless of whether the tissue was of adult or of embryonic type, nor did the condition of the growth of the tissue in the culture influence the stability of the phage. The tissue cells were not injured by the presence of the mouse typhoid phage. In tissue cultures containing phage alone or in conjunction with mouse typhoid bacilli, the phage was not inactivated even though it did not exhibit its lytic action in the cultures.

AUTHORS' SUMMARY.

PARASITIC CIRRHOSIS OF THE LIVER IN A CAT INFECTED WITH OPISTHORCHIS PSEUDOFELINEUS AND METORCHIS COMPLEXUS. HIRAM E. ESSEX and JESSE L. BOLLMAN, Am. J. Trop. Med. **10**:65, 1930.

The clinical course, as well as the histologic picture of the disease, appeared to be true biliary cirrohsis of the type described by Hanot; it was quite different from the cirrhosis of Laennec or from obstructive jaundice. The hyperplasia of the biliary duct system suggested some specific cause associated with parasitic infection. In this event, the specicity must be closely associated with the parasites because obstructive jaundice with the usual types of bacillary infection of the bile ducts does not produce extensive hypertrophy. Since the hyperplasia extended into the smaller bile ducts, in which parasites or ova could not migrate, it would appear that the specific irritant either extended up the biliary channels by diffusion or reached the finer bile ducts by way of the portal vein. The latter hypothesis seems more probable in view of the fact that other forms of cirrhosis are produced by intestinal absorption of more or less specific hepatotoxic agents.

AUTHORS' SUMMARY.

LIVER AUTOLYSIS IN VIVO. J. C. ELLIS and L. R. DRAGSTEDT, Arch. Surg. **20**:8, 1930.

In a series of experiments on dogs, the authors demonstrated that the autolysis which takes place when uncontaminated liver is deprived of its circulation and allowed to float free in the peritoneal cavity is due to the combined action of the anaerobic organisms and intracellular enzymes. All of the dogs in which the liver was ligated or pieces of liver placed in the peritoneal cavity died in less than forty-eight hours, and the majority in less than twenty-four hours. The liver becomes spongy and gas-filled. Cultures under anaerobic conditions gave a growth of gram-positive, anaerobic bacilli. In one series of experiments, cultures were made of the liver first, and the same organisms recovered postmortem as were recovered in the culture. If the liver was autoclaved and thus sterilized, no ill effects were produced on the dog, and very little autolysis of the liver took place. The authors conclude that so-called in vivo aseptic autolysis of the liver is always accompanied by anaerobic infection, and that the anaerobic organisms are always present in living, uncontaminated liver. They also conclude that these organisms or their products are the immediate cause of death.

N. ENZER.

POSTVACCINAL ENCEPHALITIS AND ALLIED CONDITIONS. SIMON FLÆXNER, J. A. M. A. **94**:305, 1930.

The decade through which we are passing has shown an increase in the number and variety of myelitic and encephalitic disorders. In part this is attributable to outbreaks of epidemic or lethargic encephalitis, and in part it can be accounted for by what appear to be unusual attendances of antismallpox vaccination, measles and other infections, by inflammations of the central nervous organs. To our present knowledge of clinical and microscopic features it is hoped that knowledge of the directly inciting events may come also to be added.

AUTHOR'S SUMMARY.

THE EFFECT OF THE X-RAY ON THE NODULES OF VERRUGA PERUANA. HENRY R. MULLER and JOSEPH R. TYLER, J. Exper. Med. **51**:23, 1930.

The supposition that the x-rays would affect the developing and the developed verruga nodules experimentally induced in the monkey, has proved correct. The experiments show that the early verruga nodules when exposed to a single, properly graduated dose of the x-rays producing merely erythema of the skin, are inhibited in their evolution. Moreover, the skin of *Macacus rhesus* monkeys is modified by a single erythema dose of the x-rays in such a way that infection of it with *Bartonella bacilliformis* is rendered more difficult. These results are sufficiently striking to warrant the trial of the x-rays in suitably guarded doses in the treatment of verruga nodules in man. Should the employment of convalescent serum influence the course of Carrion's disease favorably and the use of the x-rays bring about a more certain and rapid devolution of verruga nodules in man, two practically applicable therapeutic measures will have been provided for the treatment of the two forms of the human disease.

AUTHORS' SUMMARY.

ON THE ISOLATION, CULTIVATION AND CLASSIFICATION OF THE SO-CALLED INTRACELLULAR "SYMBIONT" OR "RICKETTSIA" OF PERIPLANETA AMERICANA. R. W. GLASER, J. Exper. Med. **51**:59, 1930.

In *Periplaneta americana*, the large American roach, bacteriocytes are found in both sexes. These bacteriocytes are scattered throughout the fat tissue, and their cytoplasm is filled with micro-organisms. Evidence is presented to show that the intracellular forms are diphtheroidal bacilli. These diphtheroids are transmitted from one generation to another through the ova. A method is described whereby tissues, free from contaminants, may be obtained from *Periplaneta*. A medium and a new method, the "spotting technic," are described, by means of which initial cultures of the parasites were obtained from eggs within capsules, from ova and fat tissue bacteriocytes. Two conditions appear necessary, one to initiate adaptation to the new environment, the other to bring its complete realization to fruition. When development has been properly initiated, further adaptation occurs with successive transfers until finally certain other mediums appear suitable. Approximately 14 per cent of attempts at isolation and cultivation succeeded. All the micro-organisms isolated were studied, and it was found that three morphologically distinct types had been cultivated. In general, one host yielded only one type, but one female revealed three types and another two. One type was also isolated once from a fecal emulsion. The probable reason for this is discussed. The three types isolated were diphtheroidal bacilli resembling one another closely enough to be considered a single species but invariably offering distinct minor differences to warrant a separation into three distinct types. These three types have remained true to their original forms and sizes through fifty-two transfers. The sizes, general morphology, and tinctorial reactions of the three types cultivated correspond to the intracellular parasites of *Periplaneta americana*. The cultural and biochemical activities of the strains did not reveal any sound characters for differentiating types. Serologically, however, useful distinctions were found. Some additional evidence along immunologic lines is offered to show that the micro-organism cultivated is a representative of the identical species parasitic within *Periplaneta americana*. The evidence appears sound to the writer that the *Periplaneta* parasite has been isolated and cultivated over twenty times and that it is bacterium belonging to the genus *Corynebacterium* (the diphtheroids). For the species the name *Corynebacterium periplanetae*, nov. sp., variety *americana* is proposed. The three cultural types did not produce forms small enough to pass through the pores of Berkefeld "N" candles.

AUTHOR'S SUMMARY.

THE TRANSFORMATION OF PNEUMOCOCCAL TYPES. MARTIN H. DAWSON, J. Exper. Med. **51**:99, 123, 1930.

R forms of pneumococcus may be converted into S forms of the homologous type by the subcutaneous injection, in white mice, of large amounts of living R organism. R forms of pneumococcus may similarly be converted into S forms of the homologous type by the subcutaneous injection, in white mice, of small amounts of living organisms together with the heat-killed bacteria from large amounts of S. cultures. By these methods types II S and III S vaccines are equally effective in producing conversion when heated for fifteen minutes at 60 C., or for fifteen minutes at 100 C. Type I S vaccine is effective in producing conversion when heated for fifteen minutes at 60 C., but not when heated for fifteen minutes at 100 C. R vaccines and the vaccines of other organisms are not effective in producing conversion. All "in vitro" attempts to produce conversion by the use of vaccines have been unsuccessful. The rôle which the phenomenon of conversion may play in infectious processes is indicated. Type-specific S pneumococci may be transformed from one specific S type into other specific S types through the intermediate stage of the R form. R forms of pneumococci, derived from any specific S type, may be transformed into S organisms of other specific types by the following procedure: The subcutaneous injection, in white mice, of small amounts of living R forms together with vaccines of heterologous S cultures. S vaccines heated for fifteen minutes at temperatures between 60 and 80 C., are effective in causing R forms, derived from heterologous S types, to revert to the type of the vaccine. S vaccines heated for fifteen minutes at temperatures between 80 and 100 C. are not effective in causing R forms, derived from heterologous S types, to revert to the type of the vaccine. S vaccines heated for fifteen minutes at temperature between 80 and 100 C., may cause 2 R and 3 R cultures to revert to their original S type. S vaccines of any type, including type I, heated for fifteen minutes at temperatures between 80 and 100 C., are not effective in causing I R cultures to revert to their original S types. S vaccines heated for periods as long as two hours at 60 C are effective in causing R forms, derived from heterologous types, to revert to the type of the vaccine. A single cell R strain, derived from a type II S pneumococcus, has been successively transformed into a type III S, a type I S and a group IV S culture. Corresponding with the various degrees of "degradation" of the R form there are varying degrees of "development" of the S form. The nature of the conditions responsible for alteration of type as induced by these procedures has been investigated, and the causes responsible for the transformations are discussed. All attempts to produce transformation of type in vitro have been unsuccessful. The rôle which the phenomenon of transformation of type may play in problems of infection and epidemiology is indicated.

AUTHOR'S SUMMARY.

SURVIVAL OF VACCINE VIRUS SEPARATED FROM LIVING HOST CELLS BY COLLODION MEMBRANES. R. S. MUCKENFUSS and T. M. RIVERS, J. Exper. Med. **51**:149, 1930.

Vaccine virus, suspended in a mixture of serum and Tyrode's solution and separated by collodion membranes from a suspension of living kidney cells in serum and Tyrode's solution, remained active at 37 C. for a longer period of time than did vaccine virus incubated only in a mixture of serum and Tyrode solution.

AUTHORS' SUMMARY.

ON THE RELATION OF THE ORGANISM IN THE TUNICA VAGINALIS OF ANIMALS INOCULATED WITH MEXICAN TYPHUS TO RICKETTSIA PROWAZEKI AND TO THE CAUSATIVE AGENT OF THAT DISEASE. H. MOOSER and CLYDE DUMMER, J. Exper. Med. **51**:189, 1930.

Healthy lice became infected with *Rickettsia prowazeki* after feeding on monkeys inoculated with a strain of Mexican typhus. The same result was obtained

in 100 per cent of lice by rectal inoculation of an emulsion of tunica vaginalis of guinea-pigs reacting to the same strain. In the tunica vaginales of guinea-pigs and rats inoculated intraperitoneally with an emulsion of lice containing *Rickettsia prowazeki*, the intracellular organism constantly associated with the passage strain appeared regularly. *Rickettsia prowazeki* found in lice and the organism constantly present in the tunica of guinea-pigs and rats reacting to our strain of tabardillo are morphologically and tinctorially indistinguishable, and their modes of intracellular multiplication are alike in every respect. It is concluded that they are identical. This organism is constantly associated with the causative agent of Mexican typhus, both in mammals and in lice, and all of our attempts to separate them have failed.

AUTHORS' SUMMARY.

THE EPIDEMIOLOGY OF FOWL CHOLERA. LESLIE T. WEBSTER, J. Exper. Med. **51**:219, 1930.

The studies so far carried out indicate that the epidemiology of fowl cholera rests on essentially the same basis as that of rabbit pasteurellosis. In each instance, the severe epidemic form of infection is associated with a relatively virulent type of organism which survives with difficulty in the tissues of the host, whereas the endemic disease is associated with strains of relatively low virulence and high vegetative capacity. In fowl cholera, as in other animal diseases studied, the spread and severity of the infection appear to be controlled by the resistance of the host and the dosage of the organisms.

AUTHOR'S SUMMARY.

THE EPIDEMIOLOGY OF FOWL CHOLERA. THOMAS P. HUGHES, J. Exper. Med. **51**:225, 1930.

A bacteriologic study has been made of 210 fresh strains of *Pasteurella* obtained from typical cases of fowl cholera on seven widely separated poultry farms. The strains have proved identical in consisting of small, pleomorphic, bipolar-staining, gram-negative, nonmotile bacilli. They grew rapidly in infusion broth plus a trace of hemoglobin. They formed acid but no gas in mediums containing dextrose, saccharose and mannite; indol was produced. The strains fall into three distinct groups, according to the kinds of colonies formed by them on hemoglobin agar. The "fluorescent" colony was large, whitish and opaque and under suitable conditions exhibited marked fluorescence. The "blue" colony was smaller, clear slate-blue and nonfluorescent. The "intermediate" colony was moderately fluorescent after from fifteen to eighteen hours growth, and "blue" thereafter. It was "blue" at all times when crowded and occasionally of "ring" form. Cultures from the "fluorescent" colony developed the forms of the "blue" colony under certain conditions; otherwise, all forms were stable. Strains from "fluorescent" colonies were resistant to precipitation by acids and to sedimentation by centrifugation, and although they combined with specific antiserum, did not agglutinate. They were relatively highly virulent and occurred in flocks in which fowl cholera was epidemic. Strains from "blue" colonies were precipitated by acids over a wide range of concentration and agglutinated strongly in antiserums. They were of relatively low virulence and occurred in flocks in which fowl cholera was endemic. Strains from "intermediate" colonies varied in behavior between the "fluorescent" and the "blue" strains. They came from a flock in which fowl cholera was epidemic.

AUTHOR'S SUMMARY.

THE EPIDEMIOLOGY OF FOWL CHOLERA. THOMAS P. HUGHES and IDA W. PRITCHETT, J. Exper. Med. **51**:239, 1930.

In the experiments here presented, *Pasteurella avicida* proved incapable of inciting fowl cholera when introduced directly into the alimentary tract. On

the other hand, when introduced into the upper respiratory passages, it induced typical disease. When *P. avicida* was introduced into the nasal passage of controlled, selected chickens, some died of typical septicemic cholera, a few developed chronic pneumonias and other conditions and succumbed, a few developed localized inflammations of the upper part of the respiratory tract, such as rhinitis, roup and wattle involvement, while yet a few others became "healthy" nasal carriers. Usually, however, more than 50 per cent resisted infection. Repeated titrations of this sort gave, in general, uniform results, save that in spring and summer the mortality decreased. *P. avicida* was recovered from a number of cases of "spontaneous" roup, rhinitis and wattle disease. Groups of chickens reacted similarly to doses of virulent *P. avicida* varying from 20,000,000 to 20,000. Outside these limits, dosage exercised a marked influence on mortality.

AUTHORS' SUMMARY.

THE EPIDEMIOLOGY OF FOWL CHOLERA. IDA W. PRITCHETT, F. R. BEAUDETTE and T. P. HUGHES, J. Exper. Med. **51**:249, 1930.

Field studies of fowl cholera on two commercial poultry farms are described. One farm, previously free of cholera, was studied during an active epidemic which occurred during the winter months. The strains of *Pasteurella avicida* recovered, both at "autopsy" and from "healthy carriers," proved generally similar, and to be of the types producing "fluorescent" and "intermediate" colonies. These types are of relatively high virulence. After the subsidence of the epidemic, these strains tended to disappear. The second flock consisted of a small group of birds which had survived an epidemic of cholera the previous year, and in which the infection subsequently prevailed in endemic form. No deaths occurred during the period of observation, but the number of birds with localized lesions and the number of carriers greatly increased during the winter months. The strains of *P. avicida* were apparently of the type producing "blue" colonies, although some, as shown by their acid and serum agglutination reactions, resembled the "intermediates." These strains appeared to be spreading rather than dying out. The individual fowls differed in their response to the presence of infection: some showed localized lesions, others were carriers, while still others seemed entirely refractory.

AUTHORS' SUMMARY.

THE EPIDEMIOLOGY OF FOWL CHOLERA. IDA W. PRITCHETT, F. R. BEAUDETTE and T. P. HUGHES, J. Exper. Med. **51**:259, 1930.

An investigation of endemic fowl cholera has been made at a poultry farm in Belle Meade, N. J. The focus or reservoir of *P. avicida* proved to be the healthy pullets which had become carriers the previous year and which had been selected as the breeding stock for the ensuing season. From these carriers, the organisms spread and gave rise during the winter months to the various forms of the infection, including the carrier state, disease localized in the upper part of the respiratory tract and typical cholera. The strains of *P. avicida* were, in general, similar and of the type that forms "blue" colonies. They were all of the same low degree of virulence; no differences were demonstrable between (*a*) strains obtained from "carriers" and those obtained at "autopsy"; (*b*) strains where the infection was spreading and severe, and those where disease was rare, and (*c*) "autumn" and "winter" strains. In general, a relatively high carrier rate was accompanied by a high mortality, although in one instance, a community with high incidence of carrier, plus a probable high degree of resistance of the host suffered but little fatal infection. An attempt was made to reduce the amount of cholera by the removal of carriers. The results of this measure indicate that such a procedure is both effective and practical.

AUTHORS' SUMMARY.

TULARAEMIA IN SHEEP IN NATURE. R. R. PARKER and J. S. DADE, Pub. Health Rep. **44**:126, 1929.

The proved occurrence of *B. tularense* in the tissues of sheep in nature opens the question of the possibility of human infection from the handling of infected carcasses. Infection is definitely possible through the primary contamination of the hands with the tissues of crushed infected ticks held in the wool or with thick excrement which is commonly present in large masses. The fingers might also become contaminated by contact with necrotic tissue which sometimes develops at the points where infected ticks have been attached. The chance that infected meat might reach the markets and be a source of danger to persons in slaughterhouses and packing houses and to the consuming public seems less likely, but cannot be altogether dismissed, especially if animals are slaughtered for immediate local consumption.

Further and more carefully planned field and laboratory observations of tularemia in sheep caused by the wood tick are desirable, (1) to determine the extent to which it is concerned in wood-tick-caused pathologic conditions, (2) to determine the geographical limits of the occurrence, which certainly are wider than indicated by present data, (3) to secure more detailed epidemiologic, symptomatologic, and pathologic data and (4) to determine whether the meat of infected slaughtered sheep is a possible source of human infection.

AUTHORS' SUMMARY.

THE SELECTION OF A HEAT-RESISTANT STRAIN OF VACCINE VIRUS (RABBIT TESTICULAR). CHARLES ARMSTRONG, Pub. Health Rep. **44**:1183, 1929.

Through continued selection and propagation, a strain of rabbit testicular smallpox vaccine of exalted virulence for animals has been developed which shows an increase of several hundred per cent in the period of time during which it will withstand a temperature of 37.5 C. and still give typical skin "takes" on rabbits. The sixty-first transfer is potent after holding for thirty-three days and three hours at this temperature. The selective process is being continued, since the upper limit appears not yet to have been reached.

AUTHOR'S SUMMARY.

TRANSMISSION OF FOWL-POX BY MOSQUITOES. I. J. KLIGLER and M. ASHNER, Brit. J. Exper. Path. **10**:347, 1929.

Mosquitoes transmit fowl-pox from infected to healthy chickens. The same infected insect may produce a number of consecutive infections over a period of at least sixteen days. Feeding on another animal species does not impair the infectivity of the insect. The virus appears to be localized on the proboscis. Infection may be produced readily by the inoculation of the proboscis from sixteen to nineteen days after the insect has become infected, but only rarely by the inoculation of any other part of its body. The virus of fowl-pox behaves in the same manner on infected silver pins as it does on the insect's proboscis. The possibility of direct mechanical transmission of virus, as well as other diseases in which the mode of transmission is unknown, should be more fully investigated.

AUTHORS' SUMMARY.

THE RELATION BETWEEN "GRASS DISEASE" OF HORSES AND BOTULISM. A. B. WALKER, Brit. J. Exper. Path. **10**: 352, 1929.

Eight horses were poisoned by oral administration of filtered cultures of *B. botulinus*. The minimal lethal dose by the mouth of culture type B was about 0.01 cc. for a horse of 500 pounds (0.00005 cc. per kilogram). The hypodermic minimal lethal dose of this culture for a mouse of 28 Gm. and for a guinea-pig

of 250 Gm. was 0.001 cc. (0.0036 and 0.0004 cc. per kilogram, respectively). The symptoms produced by botulism in horses are quite different from those produced by grass disease, and some of the clinical symptoms which are apparently the same in the two diseases are probably due to different causes. The postmortem observations in the two diseases are also quite different. Parasympathetic paralysis is one of the chief features of grass disease, but this does not occur in equine botulism.

AUTHOR'S SUMMARY.

LEPTOSPIRA ICTEROHAEMORRHAGIAE IN OXFORD RATS. A. D. MIDDLETON, J. Hyg. **29**:219, 1929.

In the Oxford district, 41.7 per cent of the rats were found to carry *Leptospira icterohaemorrhagiae* in their kidneys. The percentage of infection increases until the animals are mature, reaching a maximum of 56 per cent among one class of the population, but is less among the oldest rats. There is evidence that the organism is acquired comparatively early in life, and that immunity is obtained after a long period of infection.

AUTHOR'S SUMMARY.

GENERALIZATION OF VACCINE VIRUS. H. A. GINS, H. HACKENTHAL and NATALIE KAMENTZEWA, Centralbl. f. Bakteriol. **110**:115, 1929.

The authors show that after the injection of vaccine virus into the skin, the virus can be demonstrated in the tonsils of children before the pustule appears at the site of infection. In guinea-pigs and rabbits, vaccine viruses injected into the skin could be demonstrated in the mucous membrane of the upper respiratory passage from the second day after injection. Experiments in guinea-pigs make it seem probable that the presence of the virus in the mucous membranes should be regarded as a phase of generalization in as much as the virus could at the same time be demonstrated in the blood and internal organs.

PAUL R. CANNON.

EXPERIMENTS IN GUINEA-PIGS ON THE VIRULENCE OF B.C.G. LUDWIG LANGE and KARL W. CLAUBERG, Centralbl. f. Bakteriol. **110**:183, 1929.

Subcutaneous injections of 25 mg. of B C G were made into guinea-pigs, and the animals were then subjected to various types of injury such as inhalation of dust, vitamin deprivation, hunger, poisoning with diphtheria toxin and snake venom. These injuries were begun between the eighteenth and one hundred and sixty-ninth day after injection. In spite of the weakening of the animals by these means, no increase in virulence of the B C G strains was noted.

PAUL R. CANNON.

THE BEHAVIOR OF ROCKY MOUNTAIN SPOTTED FEVER VIRUS IN THE WHITE RAT AND THE WHITE MOUSE. Y. FUKUDA, Centralbl. f. Bakteriol. **111**:408, 1929.

An emulsion of spleen and testis from a guinea-pig infected with spotted fever virus was injected into twenty male white rats and eight white mice. These were then killed at intervals of time in order to determine the length of time the virus persisted. The determination was made by emulsifying testis and spleen into saline solution and injecting this intraperitoneally into guinea-pigs. The results showed that in the spleen-testis emulsion of white rats and in the spleen of the white mouse, the virus persisted for twenty-five days. On the seventh day after infection the spleen of the white rat contained 10,000 doses of virus.

PAUL R. CANNON.

A WATER-BORNE TYPHOID-LIKE EPIDEMIC CAUSED BY BACILLUS PROTEUS. K. BECKMANN and R. HÜRTHLE, Deutsche med. Wchnschr. **55**:1628, 1929.

Following the contamination of a water supply there was observed an epidemic of a mild type of gastro-enteritis. Most of the patients were ambulatory, but eighteen entered the hospital. In thirteen of these *Bacillus proteus-vulgaris* was considered responsible for the disease. In some instances, there was a slight positive agglutination reaction for typhoid or paratyphoid which usually became negative by the end of the third week. In two jaundiced patients with cholangeitis, *Bacillus proteus-vulgaris* was grown from bile obtained through the duodenal tube.

PAUL J. BRESLICH.

Immunology

PARESIS TREATED WITH MALARIA. WILLIAM MALAMUD and R. B. WILSON, Arch. Neurol. & Psychiat. **22**:1135, 1929.

Practically all patients with dementia paralytica treated with malaria show changes in the serum, though they may be of both negative and positive nature. Fifty-four patients with neurosyphilis (of which forty-eight had dementia paralytica and six, other forms of syphilis) were treated at the hospital with tertian malaria. Thirteen of these received no other treatment either before or after the malaria treatment; eighteen were previously treated by other methods but received no other treatment following the malarial method; in twenty-three, the malarial treatment was followed by some form of chemotherapy, in most cases tryparsamide. The patients were under observation for periods ranging from six to twenty-seven months and were inoculated (intravenously) by tertian malaria from other patients. The number of chills ranged from nine to twenty. Serologic examinations, including the permeability index, have been done immediately preceding malarial treatment, directly following the malarial treatment and two and six months after the conclusion of the treatment. The analyses of the serologic observations recorded shows that there is a difference between the behavior of the permeability index and that of the other serologic reactions.

The authors found that while one cannot claim a parallelism between the ordinary serologic observation and the clinical results, one can claim such between the latter and the permeability index (as determined by the Walter bromide method). For instance, the index is high in cases that show a good clinical result and is unchanged or shows a decrease in cases with a poor clinical outcome. The changes in the permeability index occur early and generally precede the clinical changes. They thus may be of prognostic value, and in cases in which the permeability index began to decrease, reinoculations with malaria have been done. However, it is not permissible to tell in cases in which index is becoming normal, whether or not the patient is going to stay well. In dementia paralytica, the authors found an increase of iron pigment in the walls of the blood vessels and in the microglia; this was probably due to an increased passage of the substance through the walls of the blood vessels themselves. In five cases of dementia paralytica in which the permeability for bromides had been determined before death and found high, the histologic studies showed the amounts of iron also high. Such a relationship evidently occurs only in dementia paralytica, for in four instances of other central nerve lesions (dementia praecox, senile dementia, two cases of psychosis with arteriosclerosis and myocarditis), it did not exist. The index in these cases was normal or low, while granules were practically absent.

G. B. HASSIN.

INTRADERMAL REACTION IN THE DIAGNOSIS OF HUMAN BRUCELLIASIS. A. S. GIORDANO, J. A. M. A. **93**:1957, 1929.

Killed suspensions of *Brucella abortus* were injected intracutaneously in twenty-five proved cases of undulant fever, producing severe local reactions by the method

employed. One hundred controls similarly injected yielded negative reactions in 99 per cent. It would seem desirable that this procedure should be carried out in all proved cases of undulant fever to determine its specificity in a larger series of cases.

AUTHOR'S SUMMARY.

ANTIMENINGOCOCCUS SERUMS. G. SCHWARTZMAN, J. A. M. A. **93**:1965, 1929.

The neutralizing potency of antimeningococcus serums can be demonstrated and quantitatively measured by means of the phenomenon of local skin reactivity.

The titer of neutralizing antibodies of serums determined by this method bears no apparent relationship to the titer of agglutinins.

It is intended to standardize further the method described and to use it for the development of therapeutic serums highly potent in neutralizing antibodies.

AUTHOR'S SUMMARY.

ASTHMA DUE TO ALTERNARIA. J. G. HOPKINS and others, J. A. M. A. **94**:6, 1930.

In the case of asthma reported here, the attacks occurred in locations in which mold spores were abundant. The patient showed extreme skin sensitiveness to a strain of *Alternaria* recovered from a house in which he had attacks. Attacks were induced in this patient by the extract of *Alternaria* in powdered form and also by the broth in which it had been grown. An attack was also induced by the dry powder of one of the *Circinella* isolated from another room in which he had attacks. He did not give any marked skin reaction to an extract of the latter fungus.

SKIN REACTIONS TO FILTRATES OF HAEMOLYTIC STREPTOCOCCI IN ACUTE AND SUBACUTE NEPHRITIS. O. C. HANSEN-PRUSS, W. T. LONGCOPE and D. P. O'BRIEN, J. Clin. Investigation **7**:543, 1929.

Skin reactions to the filtrates of hemolytic streptococci were studied in three groups of persons: (1) normal persons or patients suffering with various diseases, as controls; (2) patients with acute tonsillitis, and (3) patients with acute and subacute nephritis. In the control group, 62 per cent gave positive reactions, only 25 per cent of which were strongly positive; in the tonsillitis group, 95.4 per cent gave positive reactions, and in the nephritis group, 81.4 per cent gave positive reactions, 66.6 per cent of which were strongly positive. The positive reaction is regarded as an evidence of allergy toward the hemolytic streptococcus or its products. This allergy may play a rôle in nephritis.

FROM THE AUTHORS' SUMMARY.

INTRADERMAL IMMUNIZATION OF MONKEYS WITH ONE SET OF INJECTIONS OF POLIOMYELITIS VIRUS: C. P. RHOADS, J. Exper. Med. **51**:1, 1930.

By means of a single large dose of poliomyelitis virus, distributed at a number of intradermal sites, active immunity has been produced in *Macacus rhesus* monkeys, as shown by skin neutralization and intracisternal tests. In the small series (four animals) of monkeys so treated, neither abortive nor paralytic signs of experimental poliomyelitis appeared.

AUTHOR'S SUMMARY.

THE RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMMUNITY. CLAUS W. JUNGEBLUT, BARBARA R. MCGINN and GLADYS NEWNAN, J. Exper. Med. **51**: 5; 15, 1930.

Blockade of the reticulo-endothelial system by means of a single injection of india ink caused a marked retention of neoarsphenamine in the blood of guinea-pigs during the first twenty minutes of observation after intravenous injection, as contrasted with the rapid disappearance of the drug from the blood of normal controls. Rabbits blocked by a single dose of india ink showed a slower elimination of the

drug from the circulation following the first few hours after intravenous injection than corresponding controls. The arsenic content of the liver of mice, which received neoarsphenamine intravenously after a preceding blocking injection with india ink, was appreciably lower than the arsenic content of the normal organ under similar experimental conditions. Guinea-pigs blocked by intravenous injection of either india ink or trypan blue succumbed with fatal shock after the intravenous injection of heterophile immune serum, although the time of death was somewhat delayed as compared with normal controls. Local blockade of the skin of guinea-pigs with trypan blue inhibited completely the development of the characteristic skin reaction following intracutaneous injection of Forssman serum within the blocked area. Infiltration of the skin of guinea-pigs with india ink afforded no protection against the full development of the toxic skin reaction.

AUTHORS' SUMMARY.

THE RECOVERY OF VACCINE VIRUS AFTER NEUTRALIZATION WITH IMMUNE SERUM. PERRIN H. LONG and PETER K. OLITSKY, J. Exper. Med. **51**:209, 1930.

When vaccine virus and its specific antiserum are brought together, no evidence of stable union between them can be determined by the experimental methods employed. A definite relationship exists between the degrees of dilution of a neutral vaccine virus-antiserum mixture and the size of the lesion produced by endermic inoculation of such a mixture into rabbits.

AUTHORS' SUMMARY.

EARLY PULMONARY LESIONS IN PARTIALLY IMMUNE ALCOHOLIZED MICE FOLLOWING INHALATION OF VIRULENT PNEUMOCOCCI. ERNEST G. STILLMAN and ARNOLD BRANCH, J. Exper. Med. **51**:275, 1930.

The examination by means of serial sections, of 71 partially immune alcoholized mice which were killed at intervals following the inhalation of virulent pneumococci showed pulmonary localization in 7, or 9 per cent. In the case of the mouse, the initial lesion of pneumococcus pneumonia is in the alveolar wall, and the exudate into the alveolar lumen occurs secondarily.

AUTHORS' SUMMARY.

THE IMMUNOLOGICAL SPECIFICITY OF CHEMICALLY ALTERED PROTEINS. HALOGENATED AND NITRATED PROTEINS. ARTHUR WORMALL, J. Exper. Med. **51**:295, 1930.

The serologic properties of iodoproteins prepared by a method which involves less drastic treatment of the protein than the methods previously used confirm the observations of Obermayer and Pick and later authors, that iodination of proteins results in a more or less complete loss of species specificity and that a new specificity characteristic for iodoproteins is produced. A serologic investigation of brominated proteins has been made for the first time. These preparations are only slightly different from iodized proteins in their serologic properties. Evidence is submitted which indicates that the radical in iodoproteins which is responsible for the specificity is not iodine but the 3:5 dihalogenated tyrosine grouping. Thus, marked inhibition of the iodoprotein (or bromoprotein) precipitin reactions is effected by 3:5 dihalogenated tryosine, not by iodophenol or potassium iodide. A reinvestigation has been made of the serologic properties of nitrated and diazotized proteins. Proteins nitrated by nitric acid, or by a method which does not appear to have been used for proteins hitherto, namely, nitration with tetranitromethane in neutral or slightly alkaline solution, acquire a new common serologic specificity. The nitrated proteins and diazotized proteins show, in confirmation of the results of Landsteiner and Prasek and in contrast to the findings of Obermayer and Pick, little difference in their reactions. Thus diazotized proteins and proteins nitrated by either of the two methods mentioned react equally well with any nitroprotein antiserum. This interaction exists in spite of the difference in the substituents, either because the substitution with the nitro-group or the diazo-group occurs in the same position in the aromatic nucleus, possibly in the ortho-position to the

hydroxyl group, or because of some other structural similarity. In the last connection, it is suggested that both compounds may have a quinoid structure, as has been assumed for orthonitrophenols. While this assumption could account for the marked serologic difference of nitrated and halogenated proteins, it should also be mentioned that iodination (and bromination) lead to a disubstitution of halogen in the two ortho positions relative to the hydroxyl group of the tyrosine, whereas nitration of proteins probably results in the formation of mononitrotyrosine and substitution in the tryptophane group as well. It is probably impossible, therefore, to draw a strict analogy between nitration (or diazotization) and halogenation of proteins, since a comparison of their immunologic properties is not exactly a comparison of the effect of substituting a different group in the same position. Accordingly, it would appear that as yet no definite conclusions can be drawn as to the serologic effect of differences in the chemical nature of various substituents in the aromatic nucleus, although some influence is likely for general reasons. All of the chemically altered proteins still retain a small amount of the original species specificity, and the antiserums always react to a slightly greater extent with the homologous antigen than with similarly treated antigens prepared from heterologous serums. This difference occurs even when the possibility of some unaltered protein's being present in the antigen can be practically excluded.

AUTHOR'S SUMMARY.

THE BACTERIAL GROWTH INHIBITOR (LACTENIN) OF MILK. F. S. JONES and HENRY S. SIMMS, J. Exper. Med. **51**:327, 1930.

In this paper, the substance in milk which inhibits bacterial growth is called lactenin. It is stable for one and a half hours at p_H 4 and at p_H 10 and for longer periods in neutral solution. It is not associated with salts and carbohydrates and may be separated from them by dialysis. Lactenin is removed by agents which precipitate the proteins of whey. Part of these proteins may be hydrolyzed by tryptic digestion, and the resulting split products, together with the salts and sugar, may then be removed by dialysis without appreciable loss of lacteninic activity. This dialysis may be performed in a concentrating dialyzer, under sterile conditions and at low temperature, thus reducing the solution to small volume. The material may then be completely desiccated and kept three months with practically no loss of activity. The residue, on treating this dried material with salt solution, is 200 times as active as the original milk, on a dry weight basis. The size of the hemolytic zones of the scarlet fever streptococcus grown on a medium containing lactenin is found to furnish a simple and reliable measure of lacteninic activity.

AUTHORS' SUMMARY.

CHOLESTEROL AND ERGOSTEROL IN FIXATION TEST FOR SYPHILIS. E. MALTANER, J. Immunol. **18**:11, 1930.

The sensitizing action of cholesterol is not due to ergosterol, which itself has sensitizing power.

THE TOXICITY OF HUMAN SERUM FOR THE GUINEA PIG AS AFFECTED BY ABSORPTION OF AGGLUTININS. I. DAVIDSOHN and SUSAN GRIFFITH RAMSDELL, J. Immunol. **18**:23, 1930.

Serums from persons treated with immune serums and showing a toxicity of the heterophilic type for the guinea-pig, when treated with the red cells of this animal for the removal of agglutinins do not lose such toxicity. When the same serums are absorbed in the same way with sheep cells, as a heterophilic antigen, the toxicity is usually, but not always completely, removed thereby. The experiments further indicate the heterophilic nature of the antibodies concerned in the toxicity. But there is also the possibility that in these cases sheep cells constitute an incomplete antigen, or that another factor, as yet unidenified, is contained in such serums.

AUTHORS' SUMMARY.

THE ACTION OF A CYTOTOXIC ANTISERUM ON TISSUE CULTURES. J. S. F. NIVIN, J. Path. & Bact. **32**:527, 1929.

Cytotoxic properties were developed in rabbit's serum as a result of injections of suspensions of mouse embryos. Early evidence of cytotoxic action was shown by the inhibition of emigration of fibroblasts in tissue cultures; later actively growing cells were killed after exposure to the serum and never exhibited further growth when transferred to suitable mediums. Slow death of cells was followed by autolysis; rapid death seemed to inhibit autolysis. Experiments on normal epithelial and carcinoma cells produced changes in staining reaction. The carcinoma cells became shrunken, their cytoplasm clear and incapable of staining and the nuclei pyknotic. The cytotoxic activity of the serum was greatest in the presence of complement although it contained a thermostable body capable of producing a certain amount of cellular damage by itself. In addition to its cytotoxic qualities the serum was also hemolytic and precipitating. The serum had more effect on tissues of the rat than on those of unrelated species such as the rabbit, guinea-pig and chicken.

GEORGE RUKSTINAT.

SMALLPOX DURING ANTIRABIES TREATMENT. E. CONSEIL, Arch. Inst. Pasteur de Tunis **18**:387, 1929.

A boy bitten by a dog known to be rabid was first treated for rabies on the thirty-third day following the bite. He had received two injections when he developed a mild case of smallpox. Treatment for rabies was suspended for nearly four weeks, after which it was continued for twenty days. The patient recovered without symptoms of rabies.

M. S. MARSHALL.

PROPHYLACTIC IMMUNIZATION OF APES WITH B.C.G. AND SCHRÖDER'S VACCINE. O. KIRCHNER and E. A. SCHNEIDER, Beitr. z. Klin. d. Tuberk. **72**: 109, 1929.

In these experiments, thirteen mamadryas pavianes were used. Four animals were immunized with 50 mg. B.C.G., four animals were immunized three times with Schröder's vaccine, and five animals were kept as controls. Two and one-half months after immunization, all animals were infected intracutaneously with 0.003 mg. of tubercle bacilli. The development of tuberculosis was definitely delayed in the B.C.G. animals, but not prevented; their period of survival was definitely longer than that of the other two groups. Schröder's vaccine did not exert a noticeable influence on the virulent reinfection.

MAX PINNER.

ATTEMPTS TO ALTER THE COURSE OF SPONTANEOUS TUBERCULOSIS IN RHESUS MACACUS BY PROPHYLACTIC VACCINATION WITH B.C.G. H. H. KALBFLEISCH and A. NOHLEN, Beitr. z. Klin. d. Tuberk. **72**:121, 1929.

The general plan of this study was to expose both vaccinated and nonprepared control animals to a tuberculous infection through coresidence with a monkey which had been made tuberculous by an intrapulmonic injection of tubercle bacilli. Three vaccinated and three control animals were kept in cages in the open air; eight vaccinated animals and an equal number of control animals were kept in cages in heated stables. The interval between immunization and exposure varied between two weeks and seven months. The period of exposure varied between one and twenty-three days. Of eleven B.C.G. animals, five developed tuberculosis; of eleven controls, five developed the disease. All six animals, three vaccinated and three normal, which were kept in the open air failed to develop tuberculosis (period of exposure eleven and eighteen days). Of the sixteen animals which were kept in warm stables, ten developed tuberculosis, including five controls and five vaccinated animals.

Conclusions: B.C.G. proved to be harmless for the animals studied in this regard. An immunizing effect was not observed under the stated conditions.

MAX PINNER.

ON THE FORMATION OF ANTIBODIES IN THE POSTERIOR CHAMBER. J. KIMURA, Zentralbl. f. d. ges. Ophth. **22**:164, 1929.

If serum containing precipitins is injected suboccipitally into the subarachnoid space of a normal rabbit, the precipitins are thrown out into the circulation rapidly, and seventy-two hours later no trace of them can be found in the posterior chamber.

After active immunization, hemolysins and agglutinins appear seven days after the last injection into the aqueous humor of the rabbit, and the quantity of both immune bodies is much less than that in the blood. The relative quantity rises during the course of immunization and is at its height more than thirty days afterward, counting from the date of the last injection. Meanwhile, of course, the absolute quantity of the immune bodies in the aqueous humor and in the blood decreases with the termination of the immunization. This relative increase is perhaps due to the changed permeability of the tissue and to the disappearance of antigen from the organism.

Precipitins against various serums and bacteria were found by the author in the aqueous humor of the rabbit after active immunization. Their relative quantity to that of the blood was from $\frac{1}{1.000}$ to $\frac{1}{250}$ (serum precipitin) and from $\frac{1}{1.250}$ to $\frac{1}{500}$ (bacterial precipitin).

In most cases, after a single injection of the antigen directly into the subarachnoidal space of the normal rabbit no precipitin was found in the cerebrospinal fluid (in only two of ten cases, and in weak reaction). But if these injections are repeated from two to three times, the precipitin occurs both in the blood and in the cerebrospinal fluid. The author could not decide whether the immune body was formed locally in the subarachnoidal space, or whether the precipitin filters over from the blood stream.

If the antigen is injected directly into the posterior chamber of a previously well immunized rabbit, the precipitins of the blood, because of meningeal irritation, pass over in great quantities into the posterior chamber. With the decrease in this irritation, the precipitins that have passed over are thrown out again from the posterior chamber.

The author also immunized rabbits with two kinds of antigens (beef serum and egg albumin), and then injected one kind of serum directly into the posterior chamber. For instance, if beef serum is injected and the course of the production of precipitins in the posterior chamber is followed, it can be established that the precipitin for egg albumin now disappears as early as within a week, and only the antibeef precipitin increases again and remains for some time.

This proves that the tissue cells of the periposterior chamber which previously had acquired a certain status will, through a single injection of antigen actively and persistently, form the corresponding antibody.

On the basis of the foregoing observations, the author concludes that there are two sources for the precipitin in the posterior chamber: (1) that which passes over from the blood stream, and (2) that which is formed locally in the periposterior chamber. The latter source cannot be given with complete assurance.

CHARLES WEISS.

THE CAUSE OF THE NONCOAGULABILITY OF MENSTRUAL BLOOD. M. VON FALKENHAUSEN and A. PYRGIALIS, Zentralbl. f. Gynäk. **52**:2738, 1928.

Menstrual blood obtained from the uterus with the methods of Driesen and Hermstein does not contain any complement. This lack was found to be responsible for the absence of coagulability in menstrual blood. During the menstrual period, the uterus contains an increased amount of anticomplement and antithrombin.

W. C. HUEPER.

THE TITRATION OF DIAGNOSTIC TUBERCULIN. Y. WATANABE and H. KAWAMURA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**:131, 1929.

The authors found that no reaction occurred in ninety healthy calves into which intracutaneous injections of 3 cc. of tuberculin twice diluted were made. The results were the same with healthy guinea-pigs.

If the calves were infected subcutaneously or intravenously with bovine tubercle bacilli, a positive reaction to an intracutaneous injection of tuberculin was obtained without exception, one month after infection. Guinea-pigs that were infected by intravenous injection showed no reaction the first week, but 80 per cent were positive to tuberculin by the second or third week. An intracutaneous injection of a 1:100,000 dilution into tuberculous calves generally gave positive reactions. Most of the tuberculous guinea-pigs reacted to a 1:200 dilution but not all to a 1:1,000 dilution.

The intracutaneous injection of glycerin bouillon into tuberculous guinea-pigs that showed a positive tuberculin reaction called forth a local reddening. This reaction was negative if the bouillon was diluted more than twice. Protein-free glycerin bouillon containing salt solution and 0.5 per cent phenol gave no reaction on intracutaneous injection. Tuberculin that was prepared from nonpathogenic acid-fast bacilli gave a positive reaction in tuberculous calves but to a much less degree than true tuberculin. The importance of the control of tuberculins for diagnostic purposes is indicated by the fact that in tuberculous animals a variability in reaction occurs. The authors employ for this control the intracutaneous injection method of Mantoux and Roux. Calves were found to be the best experimental animals; guinea-pigs are useful although much less responsive. For the titration a standard tuberculin is required which must give in tuberculous calves a positive reaction in a 1:10,000 dilution, and in guinea-pigs in a 1:40 dilution. For testing calves, dilutions of 1:1,000, 1:10,000, 1:100,000 and 1:1,000,000 should be used; for guinea-pigs, from 1:40 to 1:400. The amount for injection was 0.3 cc. for calves and 0.02 cc. for guinea-pigs. The standard tuberculin and the test tuberculin should be injected in two parallel rows into the skin of the abdomen; in this way the effect of tuberculin can be fairly accurately titrated.

The authors recommend this method for the control of diagnostic tuberculins. For the test at least two animals should be used in order to minimize the individual variation. The minimal dilution of the tuberculin which evokes the same reaction as the standard tuberculin should be read and the value of the tuberculin specified.

ROY C. AVERY.

Tumors

STUDY OF A MENINGIOMA IN SUPRAVITAL PREPARATIONS, TISSUE CULTURE AND PARAFFIN SECTIONS. RICHARD C. BUCKLEY and LOUISE EISENHARDT, Am. J. Path. **5**:659, 1929.

Tissue cultures have been made of twenty-two meningiomas presenting a histologic structure similar to that of the other meningiomas cultured. In twenty-one of these tumors there was an abundance of collagen, psammoma bodies and cellular whorls; certainly not the type of a tumor from which a growth of tumor cells in tissue culture could be expected. In but one instance, that in the case herein reported, has there been an outgrowth of cells which could be considered as tumor cells, although cells regarded as clasmatocytes were observed. As stated, the tumor of the case presented was considered to be a meningioma from its gross appearance and from the histologic study of both the paraffin sections and the supravital preparations. In the tissue cultures there was an abundant growth of similar cells always in the form of a reticular pattern. These cells resembled the cells of the tumor as seen in the supravital preparations. They were found not to have phagocytic properties. They were considered to be the tumor cells of the meningioma, and of mesodermal origin as their pattern of growth was like that of cells of mesodermal origin. They did not resemble cells which are fibroblastic in origin, for no substances were seen to be laid down by the cells.

AUTHORS' SUMMARY.

NEED FOR STATISTICS OF CANCER MORBIDITY. F. C. WOOD, Am. J. Pub. Health **20**:11, 1930.

The advantages from making cancer notifiable would be: Increase in knowledge of the diseases now grouped under cancer; earlier diagnosis because the physician would be checked up later if a tumor should escape prompt diagnosis; inhibition of the activities of quacks who would be exposed to publicity through the notification; improvement in death certificates, and valuable information would accumulate in regard to the rate of growth of tumors, the life-length of patients and the types of cancer that offer chances of cure. Mortality records are not as important by far as records showing the number of persons who have cancer in a community and how long they live after cancer is discovered. How otherwise can the value of operation, the roentgen rays or radium be determined accurately?

TUMORS OF THE CAUDA EQUINA. CHARLES A. ELSBERG and KATE CONSTABLE, Arch. Neurol. & Psychiat. **23**:79, 1930.

Tumors of the cauda equina form, in the experience of Elsberg and Constable, 15 per cent of all the extradural and intradural tumors. A tumor was found in the cauda equina in twenty-eight of forty-five cases studied; in two, instead of a tumor, enlarged blood vessels were found. In seventeen cases no tumor was found, and the condition was classified as inflammatory (neuritis). Two instances of each type are recorded by Elsberg and Constable with operative observations. Histologically, the tumors (sarcomas, fibroblastomas, gliomas) could not always be classified definitely, and because of their unusually large size they were named "giant" tumors. They are usually encapsulated and most likely develop within the arachnoid. Extradural tumors, derived from the bone or the intervertebral cartilages were rare (only four of the twenty-eight tumors of the cauda equina were extradural tumors). The tumors occurred in patients less than 40 years of age, while neuritis was more frequent after the fortieth year. The clinical picture was the usual combination of pain, weakness in the lower extremities, atrophies, changes in the tendo achilles reflex and urinary disturbances. Roentgenologic changes could be demonstrated in the tumors but not in the neuritis group. The spinal fluid in tumors was often xanthochromic, and the globulin and total protein contents were increased (important!) without an increase in cells; while in neuritis, xanthromia was unusual, increase of globulin was not frequent, and that of total protein was never observed. In 59 per cent of patients with tumors a positive subarachnoid block was present, and in 44 per cent of the cases of neuritis this was partial or even complete. As to the injection of iodized poppy seed oil 40 per cent, this has been done in only five patients with tumors and in three with inflammatory lesions of the cauda equina. In all the cases of tumor, the information gained from such injections was of some value, but was considered by the authors much less important than a careful neurologic examination and the study of the total protein content. The spinal puncture should be done below the usual level, as low as the fifth lumbar or even in the first sacral interspace. If no fluid is obtained, a puncture at a higher level should be tried.

G. B. HASSIN.

RETINOBLASTOMA IN HOMOLOGOUS EYES OF IDENTICAL TWINS. W. L. BENEDICT, Arch. Ophth. **2**:545, 1929.

Benedict reports the cases of twin girls, one of whom had a tumor in the left eye and the other a tumor in each eye. There are several reasons for considering these girls identical or enzygotic twins. The occurrence of the tumors in similar situations in the left eyes lends support to the theory that these tumors develop from fetal rests that probably go back to the single ovum from which such twins develop.

BILATERAL ACOUSTIC NEUROFIBROMA (FIELD SURVEY OF A FAMILY OF FIVE GENERATIONS WITH BILATERAL DEAFNESS IN THIRTY-EIGHT MEMBERS). W. J. GARDNER and CHARLES H. FRAZIER, Arch. Neurol. & Psychiat. **23**:266, 1930.

In one family (covering five generations with 217 members), thirty-eight persons developed bilateral deafness; fifteen of these subsequently became blind; in each case the blindness was preceded by vomiting. The prevailing lesion, according to the evidence obtained, was bilateral acoustic fibromas. A clinical pathologic report of a case is described by Gardner and Frazier, with an addition of a clinical report of forty-seven members of the patient's family. One patient, a man, aged 28, died three days after an operation for an acoustic tumor which was diagnosed. The necropsy revealed two tumors, one on each side. On the left side, the eighth nerve was seen to plunge into the tumor at a distance of 1.5 cm. from the point of exit from the brain stem. No tumors were found elsewhere in the brain, dura or cerebral nerves. The histologic examination showed a neurofibroma, and with the Gross-Bielschowsky staining method the nerve fibers in the tumor itself were demonstrated. Another patient, a woman, aged 26, was deaf (three years) and blind (six months), had had headaches and hallucinations of persecution; the speech was thick; the pupils did not react to light. She died with symptoms of a tumor of the brain. At necropsy, two symmetrically placed tumors were found in the pontile angles (about 1½ inches [3.8 cm.] each). According to the microscopic report, they were "probably similar to tumor of nervus acusticus." No associated evidence of von Recklinghausen's disease in the family was found. In this family, bilateral deafness was the prominent symptom and transmitted from generation to generation.

G. B. HASSIN.

GENERALIZED MELANOSIS. S. C. WAY and S. E. LIGHT, J. A. M. A. **94**:241, 1930.

A remarkably extensive generalized melanosis is described in a woman, aged 66, the primary focus apparently being a pigmented mole, 3.5 cm. in diameter, on the back. The condition set in rapidly, and in the early stages resembled purpura hemorrhagica.

CYTOLOGIC OBSERVATIONS OF A LUMSDEN RAT SARCOMA IN VITRO. E. S. HORNING and K. C. RICHARDSON, Australian J. Exper. Biol. & M. Sc. **6**:143, 1929.

The behavior of the cell types during growth in cultures in vitro was observed, and the apparent malignant component was determined.

CHEMICO-PHYSICAL STABILITY AND CANCER. ARTHUR EASTWOOD, J. Hyg. **29**:117, 1929.

The prominence recently given to the Rous sarcoma has increased the confusion of hypotheses about malignancy. With a view to clarification, one may say that there are three simple hypotheses of outstanding importance, viz.: (1) the living virus hypothesis, which regards living viruses as the actual and effective cause of both the avian and the mammalian disease; (2) the autogenous enzyme hypothesis, which ascribes both diseases to the development within living cells of an ens malignatis resembling an enzyme rather than a virus; and (3) the "chronic irritation" hypothesis, which explains mammalian malignancy on this principle and considers fowl sarcoma to be of a different nature.

In the present paper, I start with acceptance of the third hypothesis and proceed to treat the subject as part of a more general problem in cellular variation, confining myself to the influence of chemicophysical stabilization as a factor in the production of variants. After illustrating the importance of this factor as a general principle of variation, I discuss in more detail its significance in "bacteriophage" phenomena, fowl sarcoma and mammalian malignant disease. From this aspect, the "ubiquitous virus" and the mysterious ens malignatis may be replaced by a common principle determining cellular variation.

AUTHOR'S SUMMARY.

THE HISTOGENY OF TERATOMA. G. W. NICHOLSON, J. Path. & Bact. **32**:365, 1929.

A retroperitoneal cystic tumor 11.5 by 8.5 by 5 cm. was found attached to the abdominal aorta, left kidney and left suprarenal gland of a 4 months old female child. Histologically derivatives of all germinal layers were demonstrable. The nervous elements were more abundant than the epidermis and its derivatives and ependyma, in places forming a choroid plexus, lined the major cavity. Of particular interest was a metanephros which was thought to be an inclusion of the upper renculi of the child's left kidney, since the suprarenal gland was separated from this kidney by 4 cm. of tumor tissue and because only five pyramids were found in the left kidney.

GEORGE RUKSTINAT.

AFFINITY OF TUMOR CELLS FOR LEAD. N. KAWATA, Beitr. z. path. Anat. u. z. allg. Path. **82**:259, 1929.

The action of colloidal lead in causing regression of tumors has been ascribed by some to a specific affinity of the tumor cell for lead and other heavy metals. In order to determine whether tumor tissue has any greater affinity for lead than other tissues, Kawata used for the quantitative determination of lead in the tissues the extremely delicate method of von Hevesdy. A radioactive indicator, thorium B, was added to the lead chloride solution to be injected and the radioactivity of the mixture determined electroscopically. From the radioactivity of the ashed tissues after injection of the mixture, the lead content of the tissue could be determined. Mice with transplanted carcinoma were used. The tissues examined were tumor, lung, liver and kidney. The time of the examination was from twelve to seventy-two hours after the injection; examination after longer periods was not possible because the material lost its radioactivity after seventy-two hours. The tumor tissue had no greater affinity for lead than the other tissues; liver, in fact, showed a much higher lead content than tumor or the other tissues. Any action that colloidal lead may have on tumor cells is not therefore due to a greater affinity on their part for lead. It might be due to greater susceptibility to the harmful effects of lead, but necrobiotic changes were no greater in the tumors of mice into which injection was made than in those of controls. Kawata believes that the deleterious effect that colloidal metals may have on tumor tissue is due to the effect of the metal on the blood vessels of the tumor.

O. T. SCHULTZ.

CHONDROBLASTOMA GROWING IN THE VEINS. M. KÓSA, Virchows Arch. f. path. Anat. **272**:166, 1929.

In a girl, 13 years of age, a large tumor of right femur grew through the lumen of the veins into the heart, even into the sinus venosus. The pulmonary arteries filled with tumor down to the capillaries. There was no destructive growth and no metastases; the tumor could be separated easily from the vessel wall. The tumor thrombus measured 70 cm. in length from the femur to the heart. The structure was that of different forms of cartilage, mostly adult. In the veins, the tumor has lost its blood vessels. It was, so to speak, a tissue culture of cartilage rather than a tumor.

ALFRED PLAUT.

REPEATED OCCURRENCE OF SARCOMA IN A COLONY OF CHICKENS. C. CHAMPY and C. BLUMENSAAT, Virchows Arch. f. path. Anat. **272**:205, 1929.

Many tumors in chickens are overlooked unless systematic autopsies are done. In four castrated animals, one rooster and three hens, sarcoma was found. All four had been in good health before. No work with Rous sarcoma had been done in the place in question. None of the uncastrated animals developed sarcoma, and only fifteen of seventy had been castrated. The tumors developed between eight and eighteen months after operation. In the operative scars in hens small

nodules of sarcoid tissue have been observed. The authors suggest that tissue of that kind may be susceptible to some "rather unspecific and rather ubiquitous virus." One of the tumors was situated in the radix of mesentery, a rare location for fowl sarcoma. There were no metastases in the lymph nodes, but there were many small nodules in the liver and parietal peritoneum, and much ascites. The tumor was mostly myxomatous.

ALFRED PLAUT.

PRIMARY TUMORS OF THE PLEURA. EDELTRAUD KUX, Virchows Arch. f. path. Anat. **272**:650, 1929.

Three primary diffuse tumors of the pleura are described, two of them carcinomatous and one sarcomatous. The author lays stress on the intermediate character of the pleural lining cells, which in Maximow's tissue cultures have yielded epithelium as well as connective tissue. The name mesothelioma is considered best; the name endothelioma for these tumors should be abolished.

ALFRED PLAUT.

RELATION OF SEX TO TUMOR DEVELOPMENT. H. GÜNTHER, Ztschr. f. Krebsforsch. **29**:91, 1929.

Basing his conclusions on the study of a wide range of statistical material, the writer makes the following summary of the relations of sex to tumor: The undue frequency of cancer in the female is due entirely to the tendency of the female sex organs and biliary tract to this disease; in the male, there is an established greater incidence of cancer of the stomach, kidney, urinary bladder, and especially of the lip, tongue, larynx and esophagus. Cancer is more frequently missed in the male than in the female. The importance of exogenous factors in the sex distribution of cancer is usually overemphasized. Sex plays no part in the distribution of metastases, except for the high frequency of such involvement of the ovary. With sarcoma there is little difference between sexes; but sex plays a part in determining the type of tumor more likely to involve certain organs, carcinoma and hypernephroid tumors of the kidney being commoner in the male, sarcoma of that organ in the female. The female thyroid is more prone than the male to the development of miscellaneous tumors. Lipomatosis dolorosa and atrophicans are considerably more frequent in the female than in the male.

H. E. EGGERS.

THE ROFFO REACTION. L. M. CORREA, Ztschr. f. Krebsforsch. **29**:112, 1929.

The Roffo diagnostic reaction for cancer is here considered under three sections, the first dealing with the origin of the test, the second with its diagnostic value, and the third with its theoretical aspects. The writer concludes that while the test is not specific, it is of some real confirmatory value. Its cause is to be sought in a physicochemical alteration of the serum, in connection with the adsorptive power of this for carbon dioxide.

H. E. EGGERS.

THE PRODUCTION OF TUMORS BY THE BLOOD OF TUMOR ANIMALS. F. BLUMENTHAL, Ztschr. f. Krebsforsch. **29**:549, 1929.

When blood drawn from the superficial veins of the inoculable tumors of rats and mice, and less constantly that drawn from the heart, was injected into other animals, tumors were induced which in all but one case corresponded to the parent tumor. Inoculation of the serum gave negative results, but clotted blood taken up in Ringer's solution, red cells and white cells all gave positive results. There are, of course, two possible explanations: the presence of free tumor cells in the blood, or the existence of a tumor-producing agent which attaches itself to suitable colloidal material. In order to achieve positive results, the parent tumor must have attained a suitable size.

H. E. EGGERS.

STUDIES OF TUMOR CYTOLOGY. B. LIPSCHÜTZ, Ztschr. f. Krebsforsch. **29**:554 and 564, 1929.

In cases of human round cell sarcoma and in a case of nevocarcinoma, the writer found intracellular structures similar to those previously reported by him in various animal tumors. He believes that their absence in a case of lymphosarcoma may indicate a differential criterion in such tumors. From the fact that they were absent in nonmalignant nevus cells in the early case observed, he believes that their presence may be a hallmark of malignancy. Beyond this he carefully abstains from attaching to them any special significance. H. E. EGGERS.

CANCER STATISTICS OF THIRTY-FIVE YEARS. H. JUNGHANS, Ztschr. f. Krebsforsch. **29**:623, 1929.

From the autopsy statistics of the Dresden Institute, comprising 4,192 cases of cancer in 36,408 examinations, the writer derives the following principal conclusions: In this time, there has been a considerable increase in cancer in men and a slight decrease in women. In men, the organs were involved in the following relative frequencies: the digestive system, the respiratory tract, the urogenital system and other organs. In women in the hospital, the order was: the digestive tract, the urogenital system, other organs, the respiratory tract; in women in the nursing-home the frequency of the first two was reversed. In men there was a diminution of cancer of the entire digestive tract, and a considerable increase in that of the respiratory tract; in women there was a diminution of urogenital cancer and a slight increase of cancer of the digestive tract and the respiratory passages. Each bodily tract appeared to have its own age incidence; these have not changed during thirty-five years. Except for the organs peculiar to either sex, age incidence was alike in the two sexes. H. E. EGGERS.

MORPHOLOGIC STUDY OF CELL DIVISION IN CANCER CELLS IN VITRO. R. GOLDSCHMIDT and A. FISCHER, Ztschr. f. Krebsforsch. **30**:281, 1929.

Studying from the morphologic point of view the phenomena of cell division in tissue cultures of two mouse carcinomas, it was found that atypical mitoses were relatively rare, only two instances of tripolar division being observed among hundreds of mitoses. The number of chromosomes appeared to be usually reduced, since the normal count for the mouse is accepted as 40, and most of the dividing cancer cells showed chromosomes numbering from 32 to 36. Occasionally very low counts, from 24 to 28, were observed, but normal counts were not infrequent. Some very large cells showed counts in the neighborhood of 80. The number of chromosomes was not increased in the two instances of tripolar division. H. E. EGGERS.

Medicolegal Pathology

THE MEDICOLEGAL SIGNIFICANCE OF LESIONS PRODUCED BY ELECTRICITY. DOMENICO MACAGGI, Boll. r. Accad. med., Genova **1**:927, 1929.

The lesions produced by the electric current are minutely analyzed, and its physical effect, such as mechanical, thermal, etc., as well as the chemical (electrolytic) action on the tissues, is well presented. There are no characteristic appearances which can be conclusively demonstrated in instances of death by electricity. From a medicolegal point of view, in cases of electrocution one has to establish first the electric trauma and then whether the current was strong enough to produce lethal effects; further, to evaluate the eventual concurrent causes of death and finally to consider carefully the differential diagnosis between accident and suicide.

E. L. MILOSLAVICH.

INFANTICIDE BY CUTTING THE THROAT. D. PEROTTI, Riforma med. **45**:648, 1929.

Three large, deep cuts were found on the throat, shoulders and abdomen of a new-born infant. Many superficial cuts were scattered all over the body and involved only the upper layers of the skin. The wounds appeared anemic. The umbilical cord was not ligated. The cadaver was otherwise clean. All the internal organs showed pronounced anemia. The floating test of the lungs proved that the infant had breathed. It was assumed that the severe anemia was the result of the umbilical hemorrhage, and at first it could not be positively stated if the many wounds were inflicted during life or after death. In the latter instance there was the possibility of an attempt to dismember the body. It was considered that histologic examination of the lungs would solve the problem. As the wound of the throat had severed the large blood vessels of the neck and the trachea and esophagus, the blood would have reached the bronchi and been aspirated into the pulmonary alveoli if the child had been alive and breathing. If, however, the throat had been cut post mortem, the blood would not have penetrated beyond the bronchioles, due to the absence of respiratory movements. Microscopic examination of the lungs disclosed that the alveoli were filled with blood; this proved that the deep cut through the entire neck and throat was inflicted during life. The multiplicity of the cut wounds, their irregular distribution and their apparent superfluous nature led one to assume that the mother was in a perturbed state of mind.

E. L. MILOSLAVICH.

ISO-AGGLUTININ IN PERICARDIAL FLUID. F. J. HILZER, Klin. Wchnschr. **8**:2427, 1929.

The pericardial fluid may be of value in determining the blood group, especially in the case of cadavers in which the blood has undergone severe changes or in infants and fetuses. The fluid, it appears, may be even richer than blood serum in agglutinin.

STATUS THYMICUS IN SUICIDES AS MORPHOLOGIC EXPRESSION OF THE DISTURBED INTERNAL SECRETION. A. PARABUTSCHEW, Virchows Arch. f. path. Anat. **273**:134, 1929.

In twenty-five suicides, the thymus, sex glands, thyroid, hypophysis and suprarenal gland were examined. The thymus was considerably heavier than normal (compared with Hammar's figures). Some cases showed persistence of the thymus but with some increase of medulla. In others, different degrees of regression were found. There is a relation between the lack of involution in the thymus and the degree of morphologic changes in the sex glands. In the testicles the interstitial tissue was found thick, with compression of the canaliculi. Occasionally round cell infiltration was found. Leydig cells were few. In many instances spermatogenesis was absent. The status thymicus is not a part of a status thymicolymphaticus.

ALFRED PLAUT.

HISTOLOGIC CHANGES AFTER DEATH BY BURNING. WILHELM VOGT, Virchows Arch. f. path. Anat. **273**:140, 1929.

Eight cases were examined. The main changes were in the spleen and liver. Circumscribed hyaline masses were found in the walls of small arteries in the spleen. Débris of red cells and phagocytosis of red cells were seldom found. The germ centers of the spleen often contained fragments of nuclei and accumulations of epithelioid cells; these changes were found in children only. The vessels of the liver contained many leukocytes with highly fragmented nuclei. This corresponds well with the rapid decrease in the white cell count. The suprarenal glands were examined in four cases; they showed no important changes.

ALFRED PLAUT.

Technical

A Silver-Starch-Gelatin Method for the Demonstration of Spirochaetes in Single Tissue Sections. Alfred Scott Warthin, Am. J. Syph. **13**:454, 1929.

A modification of the author's previously reported method is described, by which a much higher percentage of positive results may be obtained when used on histologic lesions of syphilis. The success of the method depends on establishing a set of conditions — the most important being the hydrogen ion concentration — under which, silver precipitation takes place more rapidly on the parasite than on its surroundings, thus making possible its demonstration in the tissue. The proper hydrogen ion concentration is obtained by the use of dilute nitric acid just before placing the tissue in the silver nitrate mixture.

Pearl Zeek.

The Effect of Intrabronchial Injections of Iodized Poppy Seed Oil 40 per Cent. R. B. Bettman, J. Kelly and N. Crohn, Arch. Surg. **19**:471, 1929.

The authors worked on dogs, and found that the instillation of poppy seed oil 40 per cent did not cause any pneumonia or any cellular reaction. Most of the oil was expelled rapidly by coughing, but small amounts may remain for several months.

N. Enzer.

Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease. R. Elman, N. Arneson and E. A. Graham, Arch. Surg. **19**:943, 1929.

The authors have devised a new method for the determination of blood amylase. The method consists essentially in plotting a curve of the change in viscosity of a starch solution which is undergoing inversion under the influence of the amylase in the blood. In a series of cases showing no pancreatic symptoms and no indication of pancreatic disease, they plotted a normal value varying from 4.3 to 6.8 units. They found the same values in a series of eleven cases that came to autopsy and in which no evidence of pancreatic disease was found. In twenty-three cases giving a clinical picture of pancreatic involvement, they found an increase in blood amylase varying from 7.8 to 15 and in a few a decrease of from 0.5 to 3.1 units. Twenty-one of these cases were verified at autopsy to have some lesion of the pancreas. These observations seem to indicate that the chief source of amylase is in the pancreas, and the explanation for the increase in the blood amylase seems to reside in the increased absorption from the pancreas following obstruction to the pancreatic ducts. In those in which the low values were found, atrophy of the pancreatic parenchyma was demonstrated, and this would seem to be a late stage of pancreatic disease. Jaundice of itself did not affect the blood amylase, as shown in a series of several cases of hemolytic jaundice. The article contains the protocols of their cases studied and a detailed description of the method.

N. Enzer.

A Simplified Stain for Oxidase Granules. S. Moschkowski, München. med. Wchnschr. **76**:1800, 1929.

Fix in 90 per cent ethyl alcohol for three minutes, wash in water, flood the preparation with a freshly prepared aqueous benzidine-peroxide solution (water saturated with a crystal of benzidine, filtered, and to each cubic centimeter of the filtrate add from ½ to 1 drop of 1 per cent hydrogen dioxide [perhydrol diluted thirty times]), wash in water, and counterstain with Giemsa.

Edwin F. Hirsch.

The Meinicke Test for Syphilis. E. Meinicke, München. med. Wchnschr. **76**:1965, 1929.

Several improvements in technic are described.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, March 10, 1930

HENRY C. SWEANY, *President, in the Chair*

CAVERNOUS HEMANGIECTASIS IN NODULAR GOITER. GEORGE M. CURTIS and P. A. DELANEY.

The complete report will appear in the ARCHIVES.

CONGENITAL ATRESIA OF THE TRICUSPID ORIFICE, DEFECTS OF THE INTRAVENTRICULAR AND INTERAURICULAR SEPTUM AND BICUSPID PULMONIC VALVE. PAUL J. BRESLICH.

The complete report will appear in the ARCHIVES.

LIPOID NEPHROSIS. PHILLIP SHAPIRO.

Three cases of lipoid nephrosis were described. One had proceeded to nephrotic contraction and another was combined with amyloidosis. The pathogenesis of lipoid nephrosis was traced, and histologic criteria for it were defined. The confusion between nephrosis, nephrotic component and amyloidosis was discussed. The congo red test was described as an aid in clinical differentiation of these conditions.

HISTOLOGIC CHANGES IN THE DUODENUM OF RATS EXPOSED TO HIGH ENVIRONMENTAL TEMPERATURES. W. C. HUEPER.

In experiments with rats which I conducted several years ago to determine the effect of high environmental temperatures on the p_H of the duodenal content and the type of the duodenal bacterial flora I observed some interesting changes in the histologic preparations of the duodenums of these rats, which were kept in cages at from 40 to 41 C. The examination of the p_H of the duodenal content revealed a distinct increase above the normal level determined by examinations of control animals. Moreover there was marked increase in the number of bacteria above the normal number present and an ascendence of the colonic bacterial flora into the duodenum. The results of these original and fundamental experiments were later confirmed on dogs by Arnold in his subsequent and more elaborate studies originating from the same laboratory.

As the histologic phase of this problem has not found consideration in the work of this author and my own observations have remained thus far unpublished, I wish to supplement from a histologic point of view the bacteriologic observations reported in the literature on this subject.

The duodenums of the rats killed were removed in toto and placed in Zenker's solution. After proper technical preparation, serial sections were made. The microscopic examination of the sections showed the cylindric epithelium defective in places, especially at the crests of the folds. Occasionally small superficial ulcers were observed, restricted in their extent to the mucosa and covered by a fibrinopurulent exudate. The mucosa and submucosa contained always a more or less dense lymphocytic and leukocytic infiltration. The tissues were hyperemic.

The histologic changes in the duodenum described are interpreted as evidence of the effect of the marked disturbance of the process of duodenal self-sterilization and possibly may be due to an increased permeability of the duodenal mucosa to bacteria and their toxins. The action of the neutral or alkaline content on the duodenal epithelium may represent a contributory factor in the causation of these changes.

AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

HOWARD T. KARSNER, *Secretary*

Annual Meeting, New York, April 17 and 18, 1930

GEORGE H. WHIPPLE, *President*

THE IDENTITY OF ANIMAL ANAPHYLAXIS AND HUMAN ALLERGY (PROTEIN HYPERSENSITIVENESS). BRET RATNER and (by invitation) HELEN L. GRUEHL, NEW YORK.

The blood serums of a patient with bronchial asthma who was sensitive to horse dander and of guinea-pigs sensitized to horse dander by inhalation were passively transferred to the normal human skin and to normal guinea-pigs. Positive passive transfers were obtained both from the transfer of the human serum and from that of guinea-pig serum. This criss-crossing of the human reagin and of the anaphylactic antibody suggests that the two antibodies are identical.

SKIN REACTIONS TO THE SOLUBLE TOXIC SUBSTANCE OF THE COLON BACILLUS. BERNHARD STEINBERG, TOLEDO, OHIO.

Skin reactions to the soluble toxic substance and to the washed, killed bacterial bodies of a twenty-four hour culture of a colon bacillus were made. Reactions read at the end of twenty-four hours appeared in a large number of normal adults and children who were tested. In people with infections caused by the colon bacillus, the reactions to the soluble toxic substance and to the vaccine were either absent or greatly diminished in size and degree. It is assumed that the skin reaction is of an antigen-antibody mechanism. Only occasionally, a normal person had agglutinins against the colon bacillus. Immunization with the soluble toxic substance of the colon bacillus reduces the size and degree of the skin reaction against it. The soluble toxic substance apparently has weak antigenic properties.

PENETRATION OF ANTIBODIES IN THE CENTRAL NERVOUS SYSTEM. JULES FREUND, PHILADELPHIA.

Antibodies can be extracted from the brain and spinal cord of rabbits actively or passively immunized with typhoid bacilli.

The titers of the antibodies in the extracts of the brain and cord depend on the titer of the blood serum. In actively immunized rabbits the following numerical relationships exist between the titers of the serum and of the organ extracts: The ratio of the titer of the serum is to the titers of extract of brain and of the spinal cord about as 100 is to 0.8; the titer of the serum is to the titer of the cerebrospinal fluid as 100 is to 0.3. In passively immunized rabbits the titer of the serum is to the titer of brain and spinal cord extract as 100 is to 0.7.

The antibodies recovered from the brain are not due to the presence of blood in it for perfusion of the brain does not reduce its antibody content appreciably.

Antibodies penetrate into the spinal fluid from the blood even in the absence of inflammation of the meninges. When the penetration is completed, the following numerical relationship exists between the titer of the serum and that of the cerebrospinal fluid: 100 : 0.25.

The penetration into the cerebrospinal fluid of antibodies injected intravenously proceeds at a slow rate, being completed only several hours after the immune serum had been injected. The penetration of antibodies into the tissue of the brain occurs at a very rapid rate. It is completed within fifteen minutes.

It is unlikely that when the immune serum is injected intravenously the antibodies reach the brain tissue by way of the cerebrospinal fluid, or that the antibody titer of the cerebrospinal fluid is lower than that of the brain extract, and that antibodies penetrate faster into the tissue of the brain than into the cerebrospinal fluid.

ETIOLOGY OF PSITTACOSIS. CHARLES KRUMWEIDE and (by invitation) MARY MCGRATH AND CAROLYN OLDENBUSCH, NEW YORK.

About Jan. 15, 1930, the Department of Health became cognizant that there was illness among persons in contact with sick parrots. The first consideration, naturally, was whether or not *Bacterium psittacosis* was causing the disease. Of a total of twenty-nine sick or dead parrots received only one showed the presence of *B. psittacosis*. This parrot had died in a pet shop, and none of the persons coming in contact with it developed any sign of illness. Among the cases of illness in human beings, there were eleven who had had contact with ill parrots and who were finally considered as having cases of psittacosis. Cultural and serologic tests showed no evidence of infection by *B. psittacosis*. The agglutination tests were repeated up to one month after the onset of the disease. These observations seemed definitely to exclude *B. psittacosis* as the etiologic agent of the disease.

Fortunately, in one instance there became available an ill parrot and two ill persons who had come in contact with the parrot. Inoculation of parrots with materials from these three cases caused disease and death, and material from these parrots likewise caused death when inoculated into other parrots. When filtered through Berkefeld V filters, the organ emulsions likewise caused disease and death. Two successive filter passages with the parrot strain and with one of the human strains were successful. These results and the failure to find any common bacterial factor seemed definitely to indicate that the disease, psittacosis, was due to a filtrable virus. Mice were found to be susceptible to the virus.

After this demonstration was completed, Bedson, Western and Simpson (London) reported similar observations. Since then, Levinthal (Berlin), Armstrong, McCoy and Branham (Washington) have also demonstrated the presence of a filtrable virus.

A STUDY OF THE EFFECT OF TUBERCLE BACILLUS LIPOIDS ON THE TUBERCULIN REACTION. ESMOND R. LONG and (by invitation) ARTHUR J. VORWALD, CHICAGO.

Doses of from 0.02 to 0.05 mg. of purified soluble tuberculin protein cause an intense interstitial cellular infiltration and profound degeneration of the cells of the spermatic tubules in the testes of tuberculous guinea-pigs (tuberculin reaction). Equal doses of purified lipoids in fine colloidal suspension cause a slight interstitial wandering cell infiltration and no degeneration. Mixing tubercle bacillus fatty acid with tuberculin protein enhances the tuberculin action of the latter in that the fluid element of the exudate is greater and the amount of fibrin present is increased. No change in the intensity of cellular infiltration or necrotizing effect on the testicular tubules or spermatocytes has been noted. The increased output of fluid suggests that an increased degree of toxic action on the capillary endothelium has occurred. Ultramicroscopic examination has shown no change in the degree of dispersion of the colloidal particles incident to mixing the two colloidal preparations.

THE SPECIFIC CYTOTOXIC ACTION OF TUBERCULIN ON TISSUE CULTURE. JOSEPH D. ARONSON, PHILADELPHIA.

The specific cytotoxic action of tuberculins prepared from the various acid-fast bacteria on the bone-marrow and the spleen of tuberculous and of non-tuberculous guinea-pigs was studied by means of tissue culture.

It was found that bone-marrow and spleen of tuberculous guinea-pigs, when planted in plasma from tuberculous or nontuberculous guinea-pigs, fail to migrate and to multiply in concentrations of tuberculin prepared from either the human or the bovine type of tubercle bacillus, and on the other hand that such concentrations of tuberculin do not interfere with the migration and multiplication of cells from the bone-marrow or the spleen of nontuberculous guinea-pigs. When high dilutions of tuberculin are added to explants of bone-marrow or spleen of tuberculous guinea-pigs, migration of cells occurs but the cells are shrunken and rounded whereas the cells of tissues from the nontuberculous animals are larger, irregular in outline and vesicular.

Tuberculins prepared from the avian type of tubercle bacillus, from the various acid-fast bacilli found in fish, snakes, frogs and turtles, from several different strains of the leprae bacillus and from a number of different acid-fast saprophytes did not interfere with the migration and multiplication of the cells from explants of bone-marrow or spleen of tuberculous or of nontuberculous guinea-pigs. Similarly, tuberculoprotein, the phosphatid and the carbohydrate fraction of the human type of tubercle bacillus fail to inhibit the migration and multiplication of the cells from the bone-marrow or spleen of tuberculous or of nontuberculous animals.

The addition of plasma from a tuberculous guinea-pig to explants of the bone-marrow or spleen of a nontuberculous guinea-pig does not render such explants susceptible to the cytotoxic action of tuberculin prepared from the bovine or the human type of tubercle bacillus.

PROGRESS IN CHARACTERIZING ANTIBODIES AND ANTIBODY ACTION. STUART MUDD, BALDUIN LUCKE and (by invitation) MORTON MCCUTCHEON and MAX STRUMIA, Philadelphia.

Analysis of the mechanism by which blood serum promotes the phagocytosis of bacteria and other foreign particles has been continued. Serums which promote phagocytosis of bacteria or of red blood cells have been found invariably to cause certain definite changes in the surface properties of their homologous antigens, namely, increased cohesiveness, decreased surface potential difference and increased resistance to wetting by oil. Similarly, but with certain exceptions, the serums that cause these characteristic changes in the antigen surfaces also promote phagocytosis. The phagocytosis-promoting, agglutinating and surface effects are in quantitative correspondence. A similar striking correspondence has been found between the agglutinating, surface and phagocytosis-promoting effects caused by the euglobulin and pseudoglobulin fractions of antibacterial serums.

Following the technic of F. S. Jones, collodion particles were coated with precipitinogen and then treated with homologous precipitin serums and their protein fractions. The same serums and serum globulin fractions cause specific precipitation, agglutination or phagocytosis according to the conditions under which they are allowed to react with their homologous antigens.

Agglutinating, surface and phagocytosis-promoting effects have thus been found to be quantitatively parallel. This quantitative correspondence of the several effects of a serum or serum globulin fraction has been found both for antibacterial and for antiprotein serums and their globulin fractions. All of the effects are consequences of the deposit of sensitizing serum substances on the antigen surface. The surface deposit so produced by maximal sensitization with homologous rabbit antiserum has similar properties whether deposited on acid-fast bacteria, on erythrocytes or on precipitinogen-coated collodion particles, i. e., the sensitized surface has wetting properties characteristic of protein, is cohesive and has an iso-electric point between p_H 5.5 and 5.8. These are the properties also found for specific (immune) precipitate.

These studies thus bring evidence of a new sort in support of the following simple generalization: The combination of antigen and antibody is determined by specific chemical affinities. The effects following this combination, namely, precipitation, agglutination, changes in surface properties and phagocytosis, are consequences of the properties primarily of the antibody-protein combined with and deposited on the antigen surface.

THE BUCHNER RENAISSANCE IN IMMUNOLOGY. W. H. MANWARING, Stanford University.

There is convincing evidence that injected antigens undergo a series of biochemical "hybridizations" in animal tissues, and suggestive evidence that the resulting antigen-"hybrids" become semipermanently "symbiotic" with these tissues, both terms, of course, being used metaphorically.

There is convincing evidence that some of these antigen-"hybrids" have properties simulating those of specific antibodies, but no proof thus far that they are identical with these antibodies.

The "hybridization" metaphor, however, furnishes a logical and consistent explanation of all known facts of specific immunologic adaptation, and is the nearest approach to a complete immunologic theory that can be formulated at the present time.

There is no proof at the present time, however, that antigen "hybridization" is the only mechanism of specific immunologic adaptation, and no suggestion that such "hybridizations" are not supplemented by nonspecific functional mutations and hypertrophies.

THE CYTOCHROME OF BACTERIA. C. B. COULTER and F. STONE (by invitation), New York.

The intracellular pigment cytochrome, which is found in all living plant and animal cells except the anaerobic bacteria, was originally observed by McMunn, and was rediscovered and renamed by Keilin. The presenters studied the occurrence of this pigment particularly in the *corynebacterium* group of bacteria. The four absorption bands observed by McMunn and Keilin are found by spectroscopic examination in suspensions of living bacteria of all the members of the group. In addition is found a band lying in the red portion of the spectrum. Filtrates of cultures show no selective absorption except in the case of toxin-producing diphtheria bacilli, and in filtrates of these the intensity of selective absorption runs parallel with the amount of toxin present. The characteristic absorption spectrum may, therefore, be that of the toxin itself. It has been possible by spectroscopic examination alone of different filtrates to determine the presence and approximate the amount of diphtheria toxin.

RHINOSPORIDIUM SEEBERI: REPORT OF THIRD NORTH AMERICAN CASE. CARL V. WELLER, Ann Arbor, Mich.

The clinical and structural features of the third case of *Rhinosporidium seeberi* from North America are described. The stages of the development of the parasite, as well as the character of the accompanying granulation tissue, are illustrated, as far as is possible. The foreign body giant cell reaction, which succeeds the rupture of the old cysts, is described for the first time.

CELLULAR IMMUNITY IN ACQUIRED AVIAN MALARIA. P. R. CANNON and (by invitation) W. H. TALLIAFERRO and L. G. TALLIAFERRO, Chicago.

Previous papers in this series by Talliaferro and Talliaferro demonstrated a definite immunity to superinfection in canaries infected with *Plasmodium cathemerium* and indicated that this immunity is not associated with a humoral antibody, as serum from birds with latent malarial infections was without both protective and curative action on the development of the parasites in normal birds.

The authors presented observations on the cellular reactions in the tissues of normal birds and of ones superinfected. The tissues were fixed, sectioned and stained with Maximow's hematoxylin-eosin azur II. In the normal birds it was found that phagocytosis begins as soon as parasitized red blood cells are injected, being most pronounced in the spleen and liver, and consisting in the ingestion of the parasite-red cell combination rather than of individual merozoites. In spite of a constant rate of phagocytosis, many parasitized red blood cells escape ingestion and sporulation occurs with extension of the infection. Thus, the process advances until a crisis occurs on approximately the eighth day, after which time the rate of phagocytosis apparently exceeds the rate of reproduction and the infection becomes latent.

In the superinfection, however, the parasitized red blood cells injected are removed from the circulating blood stream extremely rapidly, so that within twenty-four hours there are few survivors to sporulate. This altered reactivity seems to be due to an actually increased number of actively phagocytic cells within the spleen and to a lesser degree in the liver. Because of this, the parasitized red cells are quickly removed from the blood and the superinfection terminated. The mechanism of the immunity, then, is an increased rate of phagocytosis by the cells of the reticulo-endothelial system, and results from an increased number of actively functioning phagocytic cells, which are present in birds with latent infections.

THE PROTECTIVE EFFECT OF SPLENIC TRANSPLANTS IN ALBINO RATS AGAINST BARTONELLA MURIS ANEMIA. DAVID PERLA and (by invitation) J. MARMORSTON-GOTTESMAN, New York.

Bartonella muris anemia is an infectious disease occurring in albino rats following the removal of the spleen. It may be transmitted into normal young rats and young rabbits by the injection of whole blood from anemic splenectomized rats, and the strain of the virus may be maintained by repeated passage in young rats.

The presenters succeeded in isolating a strain of *Bartonella muris* anemia from normal nonsplenectomized adult rats by injecting the blood of the anemic rabbit into young rats. This demonstrates the fact that the adult rat is a carrier of the virus *Bartonella muris* anemia. It is further found that splenectomy in suckling rats is not followed by *Bartonella muris* anemia since during the suckling period the rat is not a carrier of the virus.

Trypanosoma lewisi infection in normal adult rats is accompanied by *Bartonella muris* anemia. The trypanosome infection produces profound changes in the pulp tissue of the spleen. Functional injury to this pulp tissue produces the same effect in the adult albino rat as splenectomy in lowering the resistance to the *Bartonella* infection.

Less than one fourth of the spleen left in situ is sufficient to prevent the development of *Bartonella muris* anemia. Autoplastic transplants of small pieces of splenic tissue made six weeks prior to the removal of the spleen prevent the development of *Bartonella* anemia in more than 50 per cent of the rats, whereas transplants made four weeks prior to splenectomy do not protect. Histologic examination of the transplants in the animals that were protected from the anemia reveals complete regeneration of all elements of the splenic tissue, both malpighian bodies and pulp cells. In the rats that were unprotected the splenic transplants showed complete regeneration of the malpighian bodies, but exhaustion destruction of the pulp tissue. This demonstrates that the pulp cells of the spleen are specific in the protective mechanism of the rat to *Bartonella muris* anemia.

AVIAN TUBERCULOSIS IN NORMAL AND VACCINATED RABBITS. E. M. MEDLAR, Mt. McGregor, N. Y.

Virulent avian tubercle bacilli when inoculated subcutaneously into rabbits cause a local abscess which ruptures and heals. The rabbits do not develop generalized tuberculosis and do not succumb to the subcutaneous inoculation.

Rabbits inoculated intravenously with 1 mg. or more of virulent avian tubercle bacilli always succumb to the infection within from two weeks to a month. A study of the microscopic changes of such animals shows extensive involvement of the spleen, liver and bone-marrow. The cell chiefly concerned in the reaction is the mononuclear leukocyte or monocyte. Many lesions show slight abscess formation due to the participation of the neutrophil. The presence of "myeloid" giant cells, which are megalocaryocytes, in the spleen, liver and lungs, suggests a similarity between the process and Hodgkin's disease.

The daily leukocyte records of the animals show a close parallelism with the microscopic changes found. In practically every instance, the leukocyte picture became septic a short time before death occurred.

A group of rabbits, that had been inoculated six months previously with living human tubercle bacilli, was given an intravenous injection of avian tubercle bacilli, the same amount being given to a group of controls on the same diet. The injection of human tubercle bacilli had caused a local abscess which ruptured and healed, as did the subcutaneous inoculation of avian tubercle bacilli. The animals were in excellent physical condition and had normal blood counts at the time the inoculations were given.

One of these rabbits died within seven days. The remaining animals lived from four to five months. These animals showed marked involvement of the kidneys and joints. There were a few tuberculous foci in the lungs and liver. The microscopic changes were similar to those seen in chronic tuberculosis in human beings.

Daily leukocyte records showed the establishment of a septic leukocyte picture long before the death of the animal. This corresponds closely with the leukocyte picture in chronic, progressive cases of tuberculosis in human beings. Here again the leukocyte picture closely parallels the microscopic changes present.

THE USE AND THE REASONS FOR THE USE OF THIOCRESOL TO STIMULATE WOUND HEALING. STANLEY P. REIMANN, Philadelphia.

Since Hammett has shown that the sulphydryl group (—SH) is essential for cell division, this group, when presented in the proper concentration to cells, should stimulate mitosis. The healing of wounds is essentially a matter of cell proliferation; consequently —SH compounds should hasten healing. The question to which group the —SH radicle should be attached is apparently not of essential importance although it is of practical interest. Of a number of compounds tried, thiocresol proved advantageous. Theoretically, at least, when this compound is split, the small amount of cresol present tends to inhibit bacterial growth while not interfering materially with mitosis of the tissue cells. On old wounds, ulcers, etc., it is used as a wet dressing in a solution of 1 : 10,000. Certain practical points must be observed, such as the maintenance of proper growth balance between epithelium and granulations, etc.

EXPERIMENTAL STUDIES IN POLIOMYELITIS. RICHARD THOMPSON (by invitation), New York.

Efforts to adapt the virus of poliomyelitis to the rabbit organism and to produce poliomyelitis in rabbits by testicular injection and by injection into the brain after testicular passage produced no evidence that the virus could be adapted in this manner. Suggestive symptoms produced in very young rabbits were duplicated in nonspecifically treated and in uninoculated controls. The admixture of a vaccine virus adapted to the rabbit organism, with the poliomyelitis virus in similar injections and passages, did not aid the adaptation. The virus of poliomyelitis, whether alone or mixed with vaccine virus, does not survive twenty-four hours in the testicle of the rabbit.

No neutralizing substances against poliomyelitis virus could be produced in rabbits by the repeated intraperitoneal and intradermal injection of poliomyelitis virus or of poliomyelitis-vaccinia virus mixtures.

Although attempts to infect monkeys by intrastomachic injections, after bile irritation of the mucosa, were entirely negative, evidence was obtained that repeated intrastomachic injection after bile irritation may produce an appreciable degree of immunity.

No evidence could be obtained that the cellular elements of the blood contain the virus in any greater proportion than the whole blood.

SPECIFIC AND SPECIAL INFLAMMATIONS OF THE NERVOUS SYSTEM. SIMON FLEXNER, New York.

During the past twenty-five years, largely because of the extensive epidemics of meningitis, poliomyelitis and encephalitis which have prevailed in that period, much attention has been directed to infections of the central nervous organs. At the present time, attention is being concentrated on encephalitis, of the epidemic form or of the variety to which the designation "postvaccinal and allied conditions" is being applied. The important fact that herpes virus is capable of inducing encephalitis in rabbits, guinea-pigs, rats and mice, and occasionally in monkeys, has come to play a significant part in the supposed etiology of epidemic encephalitis.

The purpose of this report is to draw attention to the multiple incitants of encephalitis, and hence to distinguish between encephalitis as a clinicopathologic condition and epidemic encephalitis, which appears to be a specific infectious disease. Just as there are multiple incitants for the clinico-anatomic condition to which the term "diphtheritis" is applied, and a specific incitant of the disease diphtheria, so, probably, there are also many sources of encephalitis and, probably, a single etiologic source of epidemic encephalitis. If this view is correct, then the mere production of encephalitis in animals does not imply the experimental reproduction of epidemic encephalitis.

CHRONIC FOCI OF INFECTION PRODUCED EXPERIMENTALLY. VIRGIL H. MOON, Philadelphia.

The usual methods of animal inoculation are not suited to the study of chronic focal infections. They do not approximate the conditions present in diseases in human beings. A new method for producing foci of infection in animals is reported.

Applicators of cotton are loosely wound on no. 20 or 22 rustless wire so that slight force will slip the swab from the wire. A trocar and cannula are inserted into the region to be inoculated; the trocar is then withdrawn, leaving the cannula in place. The applicator is dipped into the material to be inoculated and is inserted through the cannula. The swab is pushed beyond the end of the cannula. Then, when the wire is withdrawn, the end of the cannula pushes off the cotton into the tissue or body cavity. The cannula is then withdrawn.

The method is a simplified procedure for implanting infection in a porous substance within the tissues. The foreign substance serves to maintain the infection against effective body resistance. The method is well suited for producing chronic foci in subcutaneous and intramuscular areas and in the body cavities. By exposing the viscera infection may be implanted in the spleen, liver, gallbladder or other structures. In such instances, a smaller cannula and correspondingly smaller applicators are used.

Dogs, which are so resistant to ordinary inoculations that they are seldom used for the purpose, are easily infected by this method. When inoculated with streptococci, masses of infected granulation tissue from 3 to 5 cm. in diameter develop in a few weeks. The inoculated organisms are regularly recovered from the area and frequently from the substance from other organs. Streptococci have been recovered in pure culture from six to ten months after implantation.

Only young dogs and rabbits have been used in these experiments. The pathologic changes resulting from these chronic foci of infection include verrucose endocarditis with rheumatic nodules in the heart musculature, the skeletal muscles and the subcutaneous tissue, acute vegetative endocarditis with multiple infarctions,

periarthritis, osteo-arthritis with anklyosis and deformity, nephritis of various forms, splenic atrophy and fibrosis, proliferative endarteritis and others.

REPORT OF THE LYMPHATIC TUMOR REGISTRY. GEORGE R. CALLENDER, Washington, D. C.

At the last report to this Society 100 cases had been contributed to the Lymphatic Tumor Registry of this Association, the period covered being approximately four years. During the past year, sixty-three cases have been received, a rate of increase of 250 per cent. I wish to take this opportunity to thank the members of this Association for this increased support. The response to my plea is gratifying, but the rate of receipt of these cases is still far below what it ought to be. Very few of the cases received during the past year have been cases in which the diagnosis was easy.

The greatest value can be reached from this Registry only if the maximum effort is made by those registering cases to follow-up the cases to their con-

Tumor Registry, 1930

Lymphosarcoma	16	
No mobilization in blood	1	
With leukemia (acute)		
Lymphoblastoma (confined to lymphatic structures)		
No mobilization in blood	0	
With mobilization in blood	15	
Leukemic	6	
Reticulum cell sarcoma	22	
(One case with lymphatic leukemia)		
Hodgkin's Disease		
Cellular	10	
Sclerosing	18	
Sarcomatous	12	
Mycosis fungoides (and tuberculosis)	1	
Lymphoblastic erythrodermia	1	
	—	102
Myelogenous leukemia	4	
Myeloma	1	
Chloroma	3	
Infectious mononucleosis?	2	
Undiagnosed	14	
Lympho-epithelioma	5	
Carcinoma	12	
Inflammation (1 tuberculosis)	7	
	—	48
		150

clusion, or over a sufficient number of years to ascertain the character of the condition. I believe that the difficulties in diagnosis and prognosis of this class of tumors are present because individuals and groups do not follow-up their cases. I further believe that we shall be able to offer definite assistance in diagnosis when and only when we have a sufficient number of cases which have been so followed-up as to determine their nature and the changes which occur during the course of the pathologic processes.

Please make an additional effort to send in, particularly, your doubtful cases.

The accompanying table presents a summary of the first 150 cases in the Registry. This summary is not intended as a classification, but it does show the divisions found to apply to the cases so far received.

HISTOLOGIC STUDIES OF THE THYROID GLAND. J. WILLIAM HINTON (by invitation), New York.

Since the question frequently arises as to what constitutes normal and abnormal thyroid tissue, sections were obtained for study from people whose deaths were due to accidental causes. The patients varied in age from stillbirth to 89 years. As a means of comparison, there were also sections from people who had died of acute and chronic diseases.

By Jan. 1, 1930, sections from 107 cases had been studied. It was intended to get sections on a large series of cases, rather than serial sections on a few cases, as these would represent more nearly the pathologic reports that are received from operative specimens. So far there have been eighty cases of accidental death from which sections of the thyroid have been studied. There were also twenty-seven cases in which the patients had died of some systemic disease; it was thought best to divide these into two groups: (1) cases of acute diseases, or in which the patient died in less than three weeks from the onset of the disease; (2) cases of chronic disease or of disease extending over months or years. There were sixteen deaths due to acute diseases, but the sections in this group failed to reveal any definite histologic changes. There were eleven patients who died of chronic diseases; no striking changes were found in the thyroid.

It was stated that sections were taken from people of various ages, and that a rather large group has been studied with the hope of finding a uniform histologic picture for normal people of different ages. So far, no conclusions have been drawn as to what is normal tissue for the different ages; the author disagrees with Hertzler's statement that: "For practical purposes I am convinced that if one keeps in mind the various changes normal to the different periods of life as above indicated, the histology of the thyroid gland will be found to be fairly constant, rendering it unnecessary to assume that it undergoes changes unknown in other organs."

In studying patients with thyroid diseases, one is at times unable to place the case in one of the groups given for the classification of goiter, such as adolescent, adenomatous or exophthalmic, and one frequently sees cases change from one type to another while under observation. From this histologic study it would also seem that a diagnosis made purely on the histologic picture without taking into consideration the clinical history and laboratory data is also open to error, and it seems that one will be forced to consider the different types of goiter merely as a stage of a continuous disease and not as a definite clinical entity, as has been believed in the past.

PSEUDOTUBERCULOSIS OF THE THYROID GLAND. PLINN F. MORSE, Detroit.

The favorable prognosis that has heretofore been attached to so-called tuberculosis of the thyroid has been the subject of frequent comment by various writers. It has been known that although the thyroid gland operated on for some type of goiter might show, on microscopic sections, large numbers of so-called tubercles, the patients usually run a favorable course and react in the usual manner to the thyroid operation, without later succumbing to tuberculous infection, either in the thyroid region or elsewhere.

The cases of so-called tuberculosis of the thyroid have usually failed to present tuberculous lesions in other parts of the body, and the postoperative search for other signs of tuberculous infection has been negative.

The cases that have been diagnosed at Harper Hospital as tuberculosis of the thyroid have run a favorable course, and all of the patients are living and well at the present time, several years after operation, with the exception of one patient, who died seven years after operation from acute intestinal obstruction—cause unknown.

The histologic study of the lesion seems to justify the assumption that probably the epitheloid reaction resembling tuberculosis is a result of either some other infection, or some metabolic disturbance which causes the colloid of the gland to assume the rôle of a foreign body. From a study of the cases, the impression was gained that the tubercle results as an effort to absorb and wall off colloid which has presumably undergone some change that makes it a foreign body. On the basis of these arguments, the presenter was inclined to think that the question of tuberculosis of the thyroid should be left open for further review, in that strong doubt is cast on the assumption that the Koch bacillus is the etiologic factor.

CHRONIC THYROIDITIS. CHARLES L. CONNOR and (by invitation) H. H. SEARLES, San Francisco.

The designation "thyroiditis" dates back to the early days of Kocher. His students, and surgeons in general, retain the name. There is some doubt, however, among pathologists as to whether such a condition actually exists. We wish to present a selected group of cases which, for want of a better name, have been classified as chronic toxic thyroiditis, and to illustrate a possible way in which they might develop.

It has long been known that acute infections and intoxications may cause degeneration of the thyroid epithelium and acini, and that as a result colloid and cell débris are spilled into the interstitial tissues. This phenomenon is usually regarded as terminal, but it is evident from a study of the literature and twenty-five cases of thyroiditis in the University of California Hospital that minor infections or intoxications, perhaps even emotional shock and overstimulation of the sympathetic system, may induce a similar degeneration of glandular elements. Since such patients do not die, there is an opportunity for a reaction to take place, and this is usually in the form of lymphoid cell infiltration or proliferation. Plasma cells and monocytes may be present; the latter, sometimes in the form of giant cells, with pseudogiant cells are formed by masses of colloid which contain the degenerate nuclei of epithelial cells.

The most constant picture is a rather diffuse desquamation of epithelium, the nuclei appearing in the previously contained colloid within the acini, and a diffuse infiltration with lymphocytes. The latter cells, as well as the plasma cells, seem to arise in situ, as evidenced by the number of mitotic figures present in them. Stages in the degeneration of thyroid epithelium appear to consist of swelling with fatty degeneration, desquamation, loss of nuclei and later a breaking down of the substantia propria, so that agglomerations of cytoplasmic masses occur. These eventually disappear, but the process in some cases becomes progressive and prolonged even after (as far as can be determined) the initial stimulus has disappeared. This tendency to progression gives rise to the condition known as chronic thyroiditis, and with the great overgrowth of lymphocytes and the concomitant proliferation of fibroblasts, the condition known as Riedl's struma may be the end-result.

Coincident with the degeneration of thyroid cells a more or less active regeneration usually takes place. This may be insufficient to take care of physiologic demands, and so symptoms of hypofunction or even myxedema may occur. Or there may be a sufficient regeneration, and therefore a histologic picture of a moderately hyperplastic gland (associated with thyroiditis), but no symptoms of thyroid dysfunction. This regeneration may proceed to any degree; a group of our cases exhibited the signs of thyroiditis (pain, pressure on the trachea, hoarseness, etc.) along with the vague symptoms of hyperfunction; another group showed histologically a marked overregeneration and hyperplasia associated with frank and definite symptoms of exophthalmic goiter. During this process of regeneration the lymphocytes gradually become less diffuse and clump together, and in late stages definite lymph follicle formation occurs—the "lymphoid exhaustion" picture of Dr. Warthin. A further stage, merely conjectured, would be a frank hyperplasia of the thyroid with characteristic lymphoid cell accumulations and without signs of thyroiditis or cellular degeneration. It would seem that a small proportion of typical thyroid hyperplasias might develop in this manner. It would be unwise, however, to infer that any considerable number pass through these stages.

STRUMA OF OVARY. ALFRED PLAUT, New York.

Three specimens of ovarian struma (from three hospitals) were studied. The time elapsed since the operations was too short for definite clinical judgment. The patients were 47, 35 and 55 years of age. The gross aspect of the specimens adds nothing new to the descriptions in the many reports in the literature. In all three specimens, other tissues were found besides the thyroid tissue, thus confirming the generally accepted opinion that the ovarian struma is a thyroideal teratoma. In

two of the specimens, all of the tissues were benign; in the one from a woman, aged 47, a large portion of the tumor was solid and gave a picture of carcinoma in the gross as well as microscopically.

The thyroid character of the ovarian struma was obvious in all three specimens. The staining qualities of the contents of the follicles were typical. The three differently colored types of secretion were found with the staining method of E. J. Kraus. Papillary protrusions with high cylindric epithelium and epithelial buds with high cells were present, giving the picture often seen in struma of the thyroid gland. It was possible to compare the structure of the malignant tumor in the one specimen with the rare type of trabecular adenoma of thyroid gland as described by Masson. The fact that this tumor was gelatinous did not preclude the possibility of its having a common origin with a thyroid-like structure. True mucin has been described in adenoma of the thyroid by Nikolsky and by Wegelin. This possibly common origin was further suggested by the fact that mucin-producing solid tumor and typical thyroid struma were intimately mixed in large areas. And, of more consequence, there were follicles in which the mucin and the typical thyroid secretion were found together. The ropy appearance of the mucin in the fixed tissue and the red color of the mucicarmine form a distinct contrast with the homogeneous, pale blue-staining thyroid secretion. It must be stated that the structure of the carcinoma-like tumor is similar also to some ovarian carcinomas, but the variety of ovarian carcinoma is so great that there is hardly any carcinoma which cannot be compared with one or another type of ovarian cancer.

All three specimens were examined for iodine. The method of Kendall and Richardson (J. Biol. Chem. **43**:161, 1920) was used. In one specimen, four analyses showed no iodine, while controls with normal thyroid gland gave figures from 1.7 to 1.88. In the second specimen, 0.025 mg. of iodine was found per gram of dried ovarian struma. This figure compares with the figures of Robert Meyer (0.014 mg.) and those of Neu (0.02 mg.). In the specimen which contained the carcinoma-like mass, the thyroid-like tissue and the solid carcinoma-like tissue were examined separately. Two analyses of the thyroid-like tissue showed 0.673 and 0.634 mg., while the solid, cancer-like tumor gave only 0.004 mg. Controls with normal thyroid showed 2.652 and 2.116 mg. Further controls were made with a carcinoma of the breast and an adenocarcinoma of the uterus. Both were negative. The figure 0.673 seems to be the highest for the iodine content of an ovarian struma ever obtained, and it seems high enough to help in asserting that these thyroid-like ovarian tumors can behave functionally in a way similar to thyroid gland. The fact that one specimen, in spite of looking exactly like the others under the microscope, contained no iodine is certainly important. (No difference could be noted in the Mallory stain.) Most of the examinations for iodine that have been reported in the literature do not reveal any iodine in the ovarian struma. In the face of the positive observations, however, it did not seem admissible to draw definite conclusions from the frequent absence of iodine. The microscopic pictures were not suggestive of embryonic thyroid tissue, which may be found free from iodine.

Some of the cystic cavities in the specimens contained material which looked different from the clear, brownish-yellow thyroid secretion in the struma-like portions. This material gave no reaction for pseudomucin. None of the specimens contained structures which could be compared with a pseudomucinous or serous cyst adenoma. Glandular structures, as may be found in any ovary that is examined in many sections, were present. No statement could be made concerning their possible connection with ovarian strumas.

The older literature on the subject deals mainly with the problem whether or not the thyroid-like tissue originated in the ovary itself. This question is settled. There remains the problem: Why does thyroid tissue occasionally grow to such large masses in the ovary? This problem is similar to the one concerning the predominance of the skin, teeth and bone in the dermoid cysts. The observations of Erwin Bauer, that in his specimen the struma started from the surface epithelium, are obviously correct, judging from the pictures given in his paper. The literature deals mainly with the general conclusions that Bauer has drawn

from his serial sections and justly disapproves of them. But the fact remains that ovarian struma can originate from the surface epithelium. With the exception of Walthardt's three specimens, no complete serial sections are reported, and therefore nothing is known concerning the relations between the surface epithelium of the ovary and the ovarian struma.

The frequent presence of ascites is clinically important because, generally, ascites together with an ovarian tumor is taken as a sign of bad prognosis, while ovarian struma has proved to be benign in most instances.

BLOOD VESSEL INVASION IN ADENOMAS OF THE THYROID GLAND. SHIELDS WARREN, Boston.

From 1923 to 1927 inclusive, thirty-four cases of adenomas of the thyroid showing definite invasion of blood vessels by clusters of tumor cells, but lacking any other evidence of a malignant condition, were found among the thyroid material received from the Lahey Clinic. Clinically, none of these cases showed any evidence of a malignant condition. Two cases showed recurrence, one in three months and one in ten months; both patients died with multiple metastases of the lungs, ten months and two years, respectively, after operation. The other thirty-two patients were living and well, from seven to two and one-half years after operation, except for one patient who died of carcinoma of the uterus two and one-half years after the thyroid operation. Thus, blood vessel invasion may be the only sign of a malignant condition in a small proportion of adenomas of the thyroid gland.

SKELETAL METASTASES IN CARCINOMA OF THE THYROID. ISAAC LEVIN, New York.

This study represents a continuation of several years of investigation of the pathogenesis of skeletal metastasis in carcinoma. The formation of these metastatic tumors in the bone, in the opinion of the author, depends not so much on the channels of transportation of the tumor emboli as on the interaction between the proliferation of the transported tumor cells and the protective resistance of the adjoining normal tissue.

The significance of the thyroid in this study is due to the phenomenon that presumably benign tumors of the thyroid and even normal thyroid tissue may form metastases.

From the clinical standpoint, the importance of the subject lies in the fact that the whole clinical symptom-complex may be due to the skeletal metastatic tumors, while the primary carcinoma in the thyroid may cause no symptoms. In the cases reported, the condition in the bone was considered clinically to be primary, and the diagnosis was made only on the biopsy material.

THE INTERACINAR EPITHELIUM OF THE THYROID GLAND. ALAN RICHARDS MORITZ, Cleveland.

By means of silver impregnation of the periacinar reticulum and wax plate reconstruction of thyroid gland, it was shown that new acini are formed by intra-acinar and extra-acinar proliferation of the epithelium. The extra-acinar proliferation is in the form of small solid or tubular buds, which, when cut tangentially, may have the appearance of rests of undifferentiated interacinar epithelium. In hyperplastic areas of normal glands and in glands the seat of pathologic hypertrophy and hyperplasia, a labyrinthine intercommunication of acini exists.

THE SIGNIFICANCE OF THE LYMPHOID TISSUE IN EXOPHTHALMIC GOITERS AND SO-CALLED TOXIC ADENOMAS. ALDRED SCOTT WARTHIN, Ann Arbor, Mich.

Exophthalmic goiter and "toxic adenoma" always present the pathologic picture of hyperplasia of the primitive lymph nodes of the thyroid, hyperplasia of the thymus and the other anatomic stigmas of the thymico-lymphatic constitution. In addition, they present certain constitutional peculiarities of their own kind. Not

all cases of thymicolymphatic constitution will present the syndrome of Graves' disease, although all cases of the latter will possess the chief anatomic stigmas of this constitution. All forms of Basedowian or Graves' symptoms represent the abnormal reactions of a primary pathologic anomaly. Basedowian or Graves' disease, "toxic goiter" and "toxic adenoma" are pathologic reactions potentially predetermined in the individual at birth by virtue of his constitutional anomaly. The potential Graves' constitution may be recognized histologically in the thyroids of very young children. To the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter and toxic adenoma I have applied the term "Graves' constitution."

THE ESSENTIAL THYROID CHANGES IN GOITER. DAVID MARINE, NEW YORK.

Perhaps the greatest difficulty in understanding and classifying the essential changes in goiter has arisen from the fact that the thyroid is a very labile tissue, capable of rapid progressive and even more rapid regressive changes in all periods of life. In the life history of most goiters there are many of these cycles, and, obviously, in a gland normally composed of retention cysts, each succeding cycle becomes morphologically more complicated and more difficult of interpretation. This tissue lability and the long duration of goiter have led to the inclusion, as Virchow pointed out seventy years ago, of a great variety of secondary and terminal degenerative changes with the essential changes.

The clue for their separation was furnished by Baumann's discovery of iodine as a normal constituent of the thyroid. The extensive studies on the relation of the morphologic changes to the iodine store, in both naturally occurring and experimentally produced goiter, which resulted from this discovery, have made it possible to work out a scheme of the sequence and relative importance of the major features of the thyroid cell and to separate the primary from the secondary changes.

Another cause of confusion has been the attempt to bring the morphologic features into specific relationship with prevailing clinical classifications of human thyroid diseases, rather than to bring the clinical classifications into relation with the morphology, which is clearly a more constant and a more natural standard. Thyroid hyperplasia is analogous to leukocytosis and has no more specific relation to metabolic diseases than leukocytosis has to infectious diseases.

Comparative studies have shown that the essential changes in goiter are similar in all the species of animals studied, and that they can be arranged in a comparatively simple scheme. When large series of human thyroids (autopsy) are studied in the light of the comparative pathology, the same cycle of changes is found, so that one can arrange these morphologic changes in a scheme that adequately presents the type and sequence of the changes which compromise the cell cycle in goiter.

The thyroid is so labile that to insist on too strict a definition of "normal" invites quibbling and defeats the object of establishing a practical standard. If the gland does not exceed 25 gm. in weight, if the follicles are filled with colloid, if the iodine store is at least 0.2 mg. per gram of fresh tissue and if the epithelium is low cuboidal, there is an adequate standard of normal.

All of the work that has been done, whether experimental regeneration following partial removal or the spontaneous or experimental production of goiter, shows that thyroid enlargement begins as a work hypertrophy and hyperplasia, and that in their developmental stages they are essentially the same for all animals. The sequence of events appears to be as follows: There are a decrease in the store of iodine, a decrease in the stainable colloid, an increase in the blood supply and a change in the epithelium from low cuboidal to high cuboidal and columnar. All gradations of this series of changes are observed from the earliest departure from normal to the extreme overgrowths of the marked hyperplasias.

Considerable confusion has arisen because pathologists have not always borne in mind the fact that progressive and regressive changes may succeed each other in rapid order and that the progressive and regressive changes are highly variable,

both in degree and in duration. Most goiters undergo hyperplasia and involution many times during their life history and each of these cycles entails certain morphologic differences which may be misleading when too great emphasis is laid on any one detail. Thus, variations in the stroma, variations in the size of the follicle and colloid content alter the blood supply and possibly the nervous control which in turn modify secondary regeneration by giving rise to patchy or insular hyperplasia.

Colloid goiter may be defined as the involution or as the return of an active hyperplasia to the condition nearest to normal, physiologically, chemically and anatomically, that a gland which has once been actively hyperplastic can assume. As is now well known, involution induced by the administration of iodine is identical with that occurring spontaneously. There is nothing degenerative or atrophic in the process of involution, although such glands may be the seat of highly degenerative or atrophic changes. Complete proof of this is established by the fact that colloid goiters regenerate as readily as normal glands following partial removal or when placed under a potent goitrogenic influence. The processes involved in the formation of a colloid goiter are the reverse of those involved in active regeneration or hyperplasia; that is, the blood supply decreases, the store of iodine rises, the epithelium becomes cuboidal and the colloid increases in density. The development of a colloid goiter by the passive dilatation of normal thyroid follicles is impossible.

While involution to colloid goiter or physiologic recovery is the usual mode of termination of compensatory hyperplasias, it occasionally happens, especially in endemic cretinism and in exophthalmic goiter, that the maximum degree of hyperplasia reached and the maximum capacity for function fail to bring about physiologic compensation, and sooner or later a state of thyroid exhaustion supervenes, that is, atrophy in spite of attempts at regeneration. The essential changes appear to be analogous to those seen in atrophic cirrhosis of the liver; that is, they are the result of long-continued hyperactivity and injury without sufficient physiologic rest. In the first stages the appearance of such a thyroid differs very little from any other extreme degree of hyperplasia, save for the increase in stroma. Later, desquamation, atrophy and necrosis result. The cells become highly variable in size and staining intensity. The nuclei also become irregular, sometimes enlarged, hyperchromatic and sometimes pyknotic. The colloid is greatly reduced, and as the process continues the follicles are reduced to nests of irregular cells in a dense stroma.

One of the secondary features of goiter in man requires especial notice, namely, the development of nodules of glandular tissue in long-standing human goiters, so-called adenomas. These growths have something in common with true tumor and usually retain many of the physiologic attributes of normal thyroid tissue. Knowledge of these growths is inadequate at the present time. The fact that they are limited almost entirely to human goiters renders experimental approach difficult. That they are an integral part of diffuse goiters is shown by the fact that all nodular goiters, in their earlier stages, were diffuse goiters. This is shown in Wegelin's well known study. As to their origin, the idea of Woeffler that they arise from fetal rests and the unfortunate term "fetal adenoma" introduced by Billroth have so influenced thyroid pathology during the last fifty years that it is difficult to undo the harm which this conception has introduced. While one cannot deny that occasionally congenital adenomas may arise from fetal rests, there can be no question that practically all adenomas arise from fully differentiated thyroid tissue and that their origin is intimately bound up with repeated hyperplasia and involution in long-standing goiters. By altering the blood supply and nervous control and through pressure effects, this process leads to insular, irregular and localized hyperplasias which eventually become so independent as to lose some of their physiologic attributes and take on certain of the characteristics of tumor.

Finally the presenter called attention to the efforts that Wegelin has been making to arrive at an acceptable international classification of the principal stages

of goiter. If the principal features could be grouped in some acceptable way, the intermediate or subgroups could be left largely to individual fancy without endangering the ability to understand what is meant. The following classification would include the essential major divisions in their sequential relations: (1) Struma diffusa: struma diffusa parenchymatosa, struma diffusa parenchymatosa et colloides, struma diffusa colloides, struma diffusa sclerosa (exhaustion atrophy); (2) Struma nodosa (adenomatosa): Struma nodosa parenchymatosa, struma nodosa parenchymatosa et colloides, struma nodosa colloides, struma nodosa sclerosa.

A Study of the Islands of Langerhans in Vivo. Benjamin N. Berg, New York.

The islands of Langerhans were studied in the pancreas of the living white mouse under iso-amyl-ethyl barbituric acid anesthesia. Microscopically, they appeared as brilliant yellowish-white bodies on the surface of the less refractile yellow pancreas or attached to veins. Accurate observations were possible only when the islands were situated at the surface of the pancreas. Great variations were encountered with respect to the number of islands that were superficial.

In suitable preparations the circulation in the islands was distinguished clearly. The capillaries appeared as thin, threadlike loops which were U, S, V or spiral shaped and which dipped into the substances of the glands. The circulation was extremely rapid, and changes were noted in the capillary pattern. Rhythmic, spontaneous contractions were observed in the small arteries.

Observations were also made concerning the action of epinephrine and pituitary extract on the blood vessels of the pancreas, including the circulation in the islands of Langerhans. Vasoconstrictor effects were noted with both drugs. In the higher order of concentrations, blanching and cessation of the circulation in the islands were observed. With more dilute solutions, the effects on the circulation in the islands were irregular and difficult to follow. Pituitary extract was tolerated by the mice in much higher concentrations than epinephrine.

The results of the studies with epinephrine and pituitary extract indicate that the circulation in the islands of Langerhans is probably regulated by changes in the afferent arterioles or the small arteries in response to physiologic stimuli.

The Changes of the Spleen in Subacute Bacterial Endocarditis. Herbert Fox, Philadelphia.

This article will be published in full in a later issue of the Archives.

Systematic Classification of Splenic Pathology. Herbert Fox, Philadelphia.

The difficulty of giving a name or classifiable description to many spleens that are chronically enlarged, received from operation or autopsy, suggested the possibility of grouping them according to a system based on numerical values given arbitrarily to the principal anatomic features. The thought grew from a request made by a surgical colleague to score spleens as epithelioma is scored. The idea was first rejected as impossible but, after an attempt had been made, the presenter found that a rough grouping occurred in two relatively easily separated groups, one showing splenomegaly, hematemesis and fibrosis, and another showing splenomegaly, purpura and pulp hyperplasia without participation of the lymph element. Mathematicians assured Dr. Fox that if the anatomic features adopted represented the correct selection and if the changes adopted were correct, it was acceptable to build formulae on their digital arrangement or on their sum. This is by way of answering the question of the numerical value of a quality, because the changes in splenic pathology would be as much qualitative as quantitative.

A large chart was made, and all of the gross characters of the whole organ and its section surface and all the characters seen under the microscope were put

into columns. If the observations were within normal limits, they were evaluated at 2; if inactive or atrophic, or less than normal, their score was 1, and if larger, more active or hyperactive in any way, the figure was 3. To this were added columns for adventitious changes, such as infarct, which were graded 0 or 1. It was soon found that scoring of the whole organs or section surfaces led to no grouping, so that the scoring was confined to microscopic observations.

The features were reduced from an original charting of 20 to 13, and this figure will have to be reduced still further. Sums of the numerical values of the characters do not permit distinct groupings of the spleens of the various forms of splenic anemia, nor do these scores differ sufficiently from those of purpura or bacterial endocarditis. In the limited group of cases of *viridans* there is a rough separation of the spleens of acute and those of more protracted cases. Thus, the more acute cases range from 12 to 15, while the more chronic examples range from 14 to 19.

The only contribution this work can offer now is that an attempt is being made to schedule organic changes in the spleen in a numerical formula with the hope that some grouping will appear. There are two further steps: the formulation, around the main characters, of the changes in less variable characters, and the comparison of numerical formulas assembled according to the clinico-pathologic diagnoses. Attempts to show that, deductively, spleens will fall into groups that have a pathologic significance have not been discarded. The features used are the following: follicles and germ centers, pulp and its splenocytes, sinuses and their endothelium, blood vessels, number and condition of the wall, fibrous tissue, reticulo-endothelial cells, blood, pigment, neutrophils and eosinophils. The adventitious characters do not receive numerical values.

A Comparison of Four Lines of Mouse Leukemia, Transmitted by Inoculation. Maurice N. Richter, New York, and (by invitation) E. C. MacDowell, Cold Spring Harbor, N. Y.

In previous communications the presenters reported the presence of an inbred strain of mice in which lymphatic leukemia occurs with great frequency, and the fact that the leukemias occurring spontaneously in this strain may be transmitted to normal young mice of the same strain by inoculation with emulsions of tissues.

From each of the spontaneous cases used as donors for the transmissions, a line of inoculable leukemia was obtained, transmissible apparently indefinitely by inoculation.

In these lines of experimental transmissions they observed varieties of manifestations similar to those occurring in spontaneous cases. Some manifestations, however, have occurred so frequently in certain lines, and infrequently in others, as to indicate the presence of differences in the inocula prepared from each.

The transmissions of the several lines were carried on in parallel experiments, the host animals being from the same inbred strain, and frequently from the same litter. Consistently reappearing differences in the lines are not, therefore, due to differences in the hosts.

Experimental Osteitis Fibrosa (Fibrosa Osteodystrophy) in Guinea-Pigs on Normal Diet, Injected with Parathormone. H. L. Jaffe and (by invitation) A. Bodansky and J. E. Blair, New York.

It has been suspected for about twenty-five years that the parathyroids are in some way related to the dystrophies of the bone. Recently Mandl, and after him others, removed enlarged parathyroids in cases of osteitis fibrosa cystica and reported rapid clinical improvement of their patients, with cessation of the negative mineral balance.

No reports have appeared on the experimental production of the fibrous osteodystrophies by the use of parathyroid extract. Nor have bone changes that fulfil the requirements for the diagnosis of osteitis fibrosa been experimentally produced by other means.

By subcutaneous injection of parathormone, the presenters regularly produced in the guinea-pig the generalized changes of the bones which satisfy all of the criteria of osteitis fibrosa, including the appearance of new bone (osteoid). The latter appears as soon as the reparative processes are permitted to operate with sufficient intensity. A guinea-pig that is permitted to go for a few days without parathormone, after previous treatment with parathormone, shows an abundance of osteoid tissue beneath the periosteum and endosteum, in the haversian canals and in the fibrous tissue in the metaphysis just distal to the epiphyseal cartilage plate.

It was necessary to use relatively large doses of parathormone to produce fibrous changes in the bones of guinea-pigs. The doses can be given to the guinea-pig without producing fatal hypercalcemia, and the animal's ability to withstand such large doses may be related to its alkaline diet.

Even one dose of 60 units when given to a guinea-pig weighing 300 Gm. produces extensive resorption, cessation of bone formation and infraction of the cortex within forty-eight hours. Such guinea-pigs may die, of extensive bone destruction, if the large doses are continued. Bone changes were produced in guinea-pigs with as little as 10 units of parathormone daily, and with from 20 to 30 units daily for two or three weeks extensive resorption and fibrosis of the bones were obtained.

In the dog, if the doses are large enough to produce rapid changes in the bones, fatal hypercalcemia may result. However, the presenters were able to prevent hypercalcemia in dogs on as much as 20 units of parathormone daily and produced in these dogs generalized bone resorption with lacunar erosion, fibrosis, cysts and osteoid tissue—criteria for the diagnosis of osteitis fibrosa cystica.

THE HISTOGENESIS AND DEVELOPMENT OF RETICULUM; ITS WIDESPREAD OCCURRENCE IN THE ADULT ORGANISM. A NEW METHOD OF DEMONSTRATION. JAMES F. RINEHART (by invitation), SAN FRANCISCO.

The method of impregnating connective tissue substance, including reticulum and collagen, was given in which there is apparently a complete impregnation of such substances and in which adequate counter-staining is achieved.

The mesenchyme was shown to possess a fibrillar cytoplasm closely related to reticulum and collagen. The differentiation of capillaries in loco in the mesenchyme and the differentiation of mesenchyme into adult connective tissue were indicated. Reticulum was shown to be a direct descendant of the mesenchyme, and evidence was presented of the probable transformation of reticulum into collagen. Reticulum fibrils were demonstrated as of universal occurrence in the capillary endothelium. Reticulum was identified with the basement membrane in the kidney, gastric mucosa and pancreas. The epithelioid cells of tuberculosis were shown to be capable of forming reticulum fibrils which may be transformed into collagen. By securing complete impregnation of this fiber substance and combining it with adequate counter-staining, a more complete concept of the capillary bed was achieved in which reticulum-lined spaces were shown to connect apparently isolated capillaries as seen by ordinary staining methods.

RAPID DIAGNOSIS OF INTRACRANIAL TUMORS BY SUPRAVITAL STUDY. LOUISE EISENHARDT (by invitation) and HARVEY CUSHING, BOSTON.

A description was given of a method of immediate diagnosis of intracranial tumors by supravital study of fresh smears. The method has been in use for the past two and one-half years; it is possible by this means to differentiate the various types of gliomas, for example, almost more easily than by the usual methods of fixed preparations.

SPONTANEOUS AND EXPERIMENTAL SCHWANNOMAS. PIERRE MASSON and (by invitation) CHARLES SIMARD, MONTREAL.

J. Nageotte has shown that if a fragment of the sciatic nerve of the rabbit is excised from one side and grafted near the intact sciatic nerve of the other side a voluminous tumor is produced by the sheaths of Schwann without participation of the axons—an artificial schwannoma. Comparative study of one of these tumors and of several spontaneous encapsulated neurinomas from man shows a complete identity of their fundamental constituents. The structure, the mode of collagen production and the manner of growth and development are the same in both types of tumor. A study of their characters shows that these constituents are different from connective tissue cells. In the building up of experimental schwannomas, connective tissue plays an important part, but in encapsulated spontaneous schwannomas the connective tissue plays only a minor part. The pure connective aspect (fibromatous, myxomatous) of certain neurinomas corresponds to the special morphologic modification of Schwann cells which have been altered by subjection to certain circulatory conditions. The palisades that are found in many spontaneous schwannomas are derived from the sheath of Schwann and are perhaps characteristic of the type of tumor derived from sensory nerves.

QUANTITATIVE OBSERVATIONS ON THE SEMILUNAR VALVES OF THE HEART. PAUL GROSS (by invitation), CLEVELAND.

A method for the determination of the surface area of valves is described. The surface area of the cusps of a semilunar valve with a large ring is commensurately greater than that of a valve with a normal ring. Valves with normal and large rings present no significant differences in the height of the cusps. Elongation of the valve rings of hearts at autopsy is associated with a decrease in the height of the cusps. It is probable therefore, that as a valve ring increases in size the cusps increase in height. The surface area of the semilunar valves is from 40 to 70 per cent in excess of a calculated minimal closing surface. The percentage of excess has no correlation with the size of the valve ring. A semilunar valve is incompetent if the average height of the cusps is equal to or less than the radius of the valve ring.

STUDIES ON THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS: I. FUNCTIONAL CHANGE OF THE RETICULO-ENDOTHELIAL SYSTEM SUBSEQUENT TO INJECTIONS OF CASEIN OR STREPTOCOCCI VACCINE. ROBERT KOCH, PITTSBURGH.

Injections of casein or killed streptococci, a prerequisite for the development of bacterial endocarditis in the experiments, led neither to degenerative changes of the endocardium nor to a transformation of the endothelial coat of the endocardium into phagocytes. Experimental studies on the vital staining of the cells of the reticulo-endothelial system, however, revealed that subsequent to injections of casein or killed streptococci the reticulo-endothelial system loses to a considerable extent the ability to develop granular deposits of dyes, if the dyes are injected in the form of solutions, while the phagocytosis of colloidal particles of the same dyes is not disturbed.

STUDIES ON THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS: II. EXPERIMENTAL PRODUCTION OF TOXIC HEART LESIONS IN THE PRESENCE OF A CHANGED FUNCTIONAL STATE OF THE RETICULO-ENDOTHELIAL SYSTEM. K. SEMSROTH, PITTSBURGH.

Experiments were carried out to determine whether or not the functional disturbance of the reticulo-endothelial system, reported in the preceding paper, influences the degree of the deleterious effect of toxic bacterial substances on the heart. Control rabbits were given doses of a diphtheria toxin or typhoid vaccine which would not lead to inflammatory reactions of the endocardium or to

myocarditis. Analogous doses were given to rabbits which previously had received a series of injections of casein or streptococcic vaccine. These animals developed a focal interstitial myocarditis. Furthermore, proliferative and exudative inflammatory reactions of the endocardium with marked degenerative changes were observed. It was inferred that the functional disturbance of the reticulo-endothelial system reported in the preceding paper was associated with an increased vulnerability of the heart to the action of bacterial products.

CHARACTERISTICS OF STREPTOCOCCI ISOLATED FROM PATIENTS WITH RHEUMATIC FEVER AND CHRONIC INFECTIOUS ARTHRITIS. R. L. CECIL and (by invitation) E. E. NICHOLLS and W. J. STAINSBY, NEW YORK.

During the past three years, streptococci have frequently been isolated from the blood and joints of patients with acute rheumatic fever and chronic infectious arthritis. The technic consisted essentially in taking large quantities of blood and in observing the cultures over a long period.

Eighty-three and three-tenths per cent of the strains isolated from cases of chronic infectious arthritis appeared to belong to one biologic group. These strains were designated as "typical strains." They seemed to fall into the alpha prime group of streptococci.

The streptococci recovered from cases of acute rheumatic fever belonged to the *Streptococcus viridans* group, although the methemoglobin formation was frequently difficult to demonstrate. Cross-agglutination tests showed that some of these organisms tended to fall into biologic groups.

Agglutination reactions with the serums of patients with chronic infectious arthritis against the antigen of any of the typical strains were very striking. The serums agglutinated to a very high titer, as high as 1:5,120 or more. This condition was not found with control serums. The serums of patients with acute rheumatic fever agglutinated some of the rheumatic fever strains to a higher titer than the serums from control cases.

HISTOLOGIC STUDIES ON THE ASCHOFF BODY. LOUIS GROSS and (by invitation) JOSEPH C. EHRLICH, NEW YORK.

In many cases the descriptions of Aschoff's bodies in the literature are confusing. There are many disagreements on the histologic appearance of these bodies, mainly because various authors depict different structures as well as different phases in the evolution of the same structure. This also accounts to a certain extent for differences of opinion concerning the origin of the cells found in the Aschoff bodies. By using various histologic methods on a large amount of autopsy material, a series of pictures was found which suggested a fairly definite life cycle for the Aschoff body. In certain cases, at least, the Aschoff body took the form of a well developed syncytium surrounding swollen collagen as one characteristic phase in the life cycle. Several phases of this cycle appeared to be pathognomonic of rheumatism. It is believed that if this cycle is thoroughly understood there will be less difficulty in recognizing these structures. The Aschoff body was shown to possess a characteristic reticulum, which also appeared to go through a recognizable life cycle.

EXPERIMENTAL STREPTOCOCCIC INFLAMMATION IN NORMAL, IMMUNE AND HYPERSENSITIVE ANIMALS. BENJAMIN J. CLAWSON, MINNEAPOLIS.

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SUBCUTANEOUS NODULES IN CHRONIC INFECTIOUS ARTHRITIS. M. H. DAWSON (by invitation) and A. M. PAPPENHEIMER, NEW YORK.

The occurrence of subcutaneous nodules in patients suffering from rheumatic fever has long been recognized and has been the subject of intensive investigation

by many workers. Less attention, however, has been paid to the subcutaneous nodules that occur in patients afflicted with rheumatoid (chronic infectious) arthritis.

During the past year in the Arthritic Clinic of the Presbyterian Hospital (supported by the Faulkner Memorial Fund), subcutaneous nodules have been observed in twenty-three patients. All of the patients presented the typical clinical picture of rheumatoid or chronic infectious arthritis. Nodules were excised from eleven of these patients and subjected to careful histologic and bacteriologic examination.

All of the material examined showed a striking, uniform and characteristic picture. The essential histologic features were summarized as follows: (1) an area of central necrosis, apparently due in its earliest stages to a gelatinous swelling and degeneration of individual collagen bundles; (2) a surrounding zone of peculiar and characteristically arranged large mononuclear cells; (3) an enclosing zone of dense and relatively avascular fibrous tissue.

The blood vessels in the area of the nodule itself rarely show significant changes, but the arterioles and capillaries in the surrounding tissue are the site of characteristic lesions.

There is a striking resemblance between the histologic appearance of these nodules and those that occur in rheumatic fever.

The results of the bacteriologic investigations have been entirely negative.

A New Meningococcus-Like Organism (Neisseria Flavescens, n. sp.) from Epidemic Meningitis. Sara E. Branham (by invitation), Washington, D. C.

Of 155 strains of meningococci isolated from cases of epidemic cerebrospinal meningitis in the United States during 1928 and 1929, 14 strains were uniformly atypical. These were among fifty spinal fluid strains received from one city during a single outbreak, thirty-six of which, or 72 per cent, fell into the four antigenic groups of Gordon's classification. The remaining fourteen, or 28 per cent, formed a homogeneous serologic group. There was no cross-agglutination with any of the four usual groups of meningococci; none of these strains was agglutinated by polyvalent commercial antimeningococcus serums.

Aside from this serologic difference, these fourteen uniform strains varied from the typical meningococci in pigment production and in total lack of fermentative ability. They did not correspond to any of the gram-negative cocci previously described.

The cases with which these strains were associated were subacute and ran a relatively long course. Eleven of the patients were given polyvalent antimeningococcus serum freely, and seven made a complete recovery.

This homogeneous group of fourteen strains does not conform with the usual conception of the meningococcus, although the strains were isolated from the spinal fluid of patients with meningitis during an epidemic in which all four of the usual serologic types of meningococci were found. To call them meningococci would alter the definition of a meningococcus and plunge the classifications of the meningococcus group into confusion. For the present this new group of fourteen strains will be referred to as *Neisseria flavescens, n. sp.*

The fact that 28 per cent of the strains isolated in one locality, or more than 9 per cent of those received from the country at large, were members of this restricted group suggests the importance of giving special attention to it.

Attempted Chemotherapy in Experimental Rabies. A. Hoyt (by invitation) and C. W. Jungeblut, New York.

A typical and constant infection was produced in white mice by the intracerebral injection of fixed virus. The animals usually showed beginning paralysis in about six days, and died on the eighth or ninth day.

In experiments involving 255 mice, which were inoculated intracerebrally with 0.02 cc. of different dilutions of virus, the approximate minimum fatal dose was a dilution of 1:320 of this virus. Although the majority of the animals given injections of amounts of virus up to as little as 1:1,280 died of rabies, a few survived. Beyond this point, the percentage of survivals increased rapidly.

Attempts were made to protect mice against rabic infection produced by intracerebral injection of one or more minimum lethal doses of fixed virus, by prophylactic treatment with silver arsphenamine, neoarsphenamine, tryparsamide, a dye-substance derived from naphthylamine-sulphonic acid (Bayer 205), plasmochin, optochin and quinine bisulphate. The drugs, with the exception of quinine bisulphate, were injected intravenously in doses as large as could be tolerated. Treatment was ordinarily started on the day of the infection; in some cases, it was continued with one or more subsequent doses of the drug.

Under the conditions of the experiment, none of the drugs used displayed the slightest prophylactic or therapeutic effect on the infection. There was, however, often a slight prolongation of the incubation period of the disease in some of the treated mice, as compared with that of the controls. This was especially noticeable with silve arsphenamine and a dye-substance derived from naphthylamine-sulphonic acid, while the incubation period appeared to be actually shortened by the administration of the quinine compounds. Caution should be used in interpreting the foregoing results, as the incubation period of a few mice, which were treated only with distilled water, was likewise slightly lengthened.

Blood Changes during Trypanosome Septicemia. Richard W. Linton (by invitation), New York.

A study of some aspects of the blood chemistry of rats with acute septicemia due to infection with *Trypanosoma equiperdum* yielded the following results: The carbon dioxide capacity of the serum was markedly lowered early in the disease. The nonprotein nitrogen and the uric acid constituents in the blood were increased in the terminal stages. The kidneys also showed terminal degenerative changes. The cholesterol remained unchanged throughout. The amount of lecithin was markedly increased, most of the observations showing a 20 to 50 per cent rise in this substance. The glycogen of the liver was lower than normal in the early stages and could not be demonstrated in the later stages of the infection. The blood sugar remained normal until a very late period in the disease.

An Experimental Study of the Effects of Heat Induced by High Frequency Alternating Currents. V. C. Jacobsen and (by invitation) K. Hosoi, Albany, N. Y.

About two years ago in a laboratory of radio research, it was noted that when a workman happened to get in the field of a short wave radio transmitter, a rise in his temperature occurred, the height of temperature depending on the time he was in the field and his proximity to the apparatus. A rise of 2.2 degrees was caused in fifteen minutes, and the response was pronounced when a water-cooled 20 kilowatt radio tube was discharging from a 6 foot rod to ground with 60,000,000 alternations per second a current of 15 kilovolts. Since diathermy with its relatively low rate of alternation of current is reputed to have valuable therapeutic applications due to the heat generated in the tissues, Dr. W. R. Whitney, director of the Research Laboratory of the General Electric Company, devised a modification of the radio transmitter which has become available for the study of experimental aseptic hyperthermia. The apparatus is a high frequency heater or oscillator on the principle of a short wave transmitter except that the energy is concentrated between two plate electrodes instead of being directed from an aerial. (Complete details of the machine are being published elsewhere.) In the experiments presented, a wave length of 25 meters was used almost entirely, an amperage of from 0.2 to 0.35 oscillating about 10,000,000 per second, a rate so rapid that no muscular contractions are produced.

Twenty-three dogs, twenty-one rats and four guinea-pigs were exposed between the plate electrodes for variable periods. A temperature once reached could be maintained either by decreasing the voltage or by increasing the distance between the electrodes. A dog's temperature taken by rectum, or determined by thermocouple, could be raised as much as 7.1 degrees in thirty-seven minutes, and 8.3 degrees in less than an hour, such rapid heating often, but not always, causing death. Three dogs were kept at about 109 F. for from five to twelve hours. Twelve dogs were given from two to nine heatings that lasted from four to thirty hours, the temperatures varying from 107 to 112 F.

The white rat and the guinea-pig could withstand about the same temperature as the dog, and the tissue changes were practically the same for the three species under the same conditions of the experiment.

After removal from the oscillator, the temperature with few exceptions returned to normal in three hours. Repeated exposures rarely gave indication of loss of control of the heat-regulating center as shown by a prolonging of the pyretic state.

While being heated, the animal would become restless, salivate, pant and perspire, and the visible membranes became congested.

In some dogs that were placed too close to the electrodes, perspiration caused arcing, which resulted in severe skin burns that healed very slowly. Rapid heating of rats often caused a disruption of the skin of the tail and severe burns at the base of the tail, with the skin finally sloughing off.

Postmortem examinations were performed as promptly as possible, since postmortem degeneration was very rapid in the highly heated tissues.

The animals that died or were killed while still at a high temperature showed the following changes: Acute congestion of all the organs occurred. In addition, the heart showed focal hemorrhage, interstitial edema and fatty degeneration of the muscle fibers. The lungs showed emphysema, atelectasis, small hemorrhages and an increased secretion of bronchial mucus. There were hemorrhages and necrosis of the lymphoid tissue of the spleen. Endothelial hyperplasia was found. Often fibrin thrombi were present in the sinusoids. A few mucosal hemorrhages and necrosis of the lymphoid tissue were present in the gastro-intestinal tract. There was an excess of mucous secretion. Mesenteric hemorrhage was found. Acute inflammation of the mucosa was often a coincident infection. The liver presented cloudy swelling, fatty degeneration, focal necrosis, focal hemorrhage and depletion of glycogen. The pancreas was normal. The kidneys showed cloudy swelling, hydrops and fatty degeneration in Henle's and convoluted tubules. The adrenals showed focal hemorrhage, and an increase in visible fat. There was hemorrhage in the capsular fat. The testes of the dogs were usually normal. The testes of the rats showed much exfoliation of the germinal epithelium and proliferation of Sertoli's cells.

One female bulldog that was heated to 108 F. for nineteen hours had a carcinoma of the breast which appeared unaffected.

The striated muscle showed glycogen depletion. The bone-marrow was hyperactive. The thyroid was normal.

The brain showed congestion, focal hemorrhage and chromatolysis of the ganglion cells. There was chromatolysis of the ganglion cells of the spinal cord.

Dogs and rats that were heated many times and in which the temperatures were allowed to return to normal showed fewer changes in their organs. Congestion was regularly present, but cloudy swelling and fatty degeneration were seen less frequently. The loss of weight was pronounced, and the fat depots showed a loss of fat. The weight was usually recovered rapidly, however, by the drinking of water. The pulmonary emphysema in the animals given one heating was probably due in part to an acidosis of the nature of lactic acid and not to ketosis.

The heat induced by this method is an internal heat probably caused, as Hosmer suggested, by an increased vibration of the molecules of the cells,

produced by their alternate attraction to each of the electrode plates in turn.

From a study of the tissues of these experimental animals, it was seen that there is little to suggest any fundamental difference between the heat induced by this oscillating current and the hyperthermia in febrile disease or that produced by external applications. Concomitant pulmonary or gastro-intestinal infection was present in slight degree in only a few animals. The dangers of the method are not entirely known. The cutaneous burns were preventable. Schereschewsky found experimental mouse cancer unfavorably influenced by this form of heating. Its application to various chronic diseases such as arthritis and dementia paralytica seems logical, and such work is under way.

The pathologic changes of fever can be studied more thoroughly than ever before by this method, and yet their clinical application must be preceded by much fundamental work, since acidosis, and later alkalosis and tetany, cloudy swelling and fatty degeneration of parenchymatous organs and deleterious effects on the germinal epithelium of testes and ovaries are definite pathologic states to be avoided in therapy if possible.

Finally, it seems in order, in this anniversary year of William H. Welch, to say that his Cartwright lectures in 1888 still constitute the greatest source of information concerning the pathology and etiology of fever, little of note having been added.

Book Reviews

IMMUNITY IN INFECTIOUS DISEASES: A SERIES OF STUDIES. By A. BESREDKA, Professor at the Pasteur Institute, Paris. Authorized translation by Herbert Child, M.R.C.S., L.S.A. Cloth. Price, $5. Pp. 364. Baltimore: Williams & Wilkins Company, 1930.

This book contains fifteen chapters. The first seven contain translations of as many articles published during the years from 1898 to 1914, inclusive. The contents of these articles are now of historical interest, and no convincing reason for republishing them at this time is apparent. The other chapters contain translations of articles published between 1922 and 1927, inclusive, except chapter 14, which carries no indication of being a reprint. In these chapters the author assumes the simultaneous rôle of scientist and advocate. The skill of the advocate may be admired, but unfortunately it cannot rescue the scientist from serious and deserved criticism. Once more the fallacy of post hoc ergo propter hoc has been given full sway. Chapter 10, for instance, on immunization by the cutaneous method, reads like the advertising pamphlet of an American manufacturer of bacterial vaccines in the balmy days of their commercial exploitation. In illustration of the beneficial effects of the local use of so-called antivirus, which is the filtrate of the culture of the microbe in question, such cases as the following are cited:

"Two months ago, Dr. M——— writes to us, I was called to a patient who had a carbuncle which began a fortnight before. I opened up with the thermo-cautery a wound occupying the whole of the nape of the neck, from one ear to the other, of the width of one's hand, full of sanguineous pus and sphacelated debris; I was truly alarmed at the sight of such a wound. I applied a dressing of broth-vaccine; 48 hours later I applied another dressing and recorded a slight improvement; the patient was more comfortable. I entrusted the three other dressings to the patient's daughter, as they lived a considerable distance from my domicile. When I returned, 10 days after the first application, I was absolutely stupefied by the result, as there was nothing to be seen but a beautifully clean wound, without the least trace of pus. Today the wound is completely cicatrised." (p. 221.)

"L——— (Francoise) was admitted into the Saint-Germain Hospital, January 5th, for an abscess of the breast, 8 to 10 days old. Very acute local pain. Temperature, 39° C. (102.2° F.). An incision of 2 cm. gave abundant evacuation of pus; streptococci were found in this. The abscess cavity was plugged with gauze saturated with filtrate vaccine. Almost immediately disappearance of pain and fever was reported. In 20 days the recovery was complete." (p. 223.)

The claim by the author that anticholera and antityphoid immunization by the buccal route may be accomplished without the production of antibodies, and that ergo must be different in nature from immunization by the subcutaneous or intravenous route, lacks the support of adequate observations. To demonstrate satisfactorily the absence or presence of antibodies in the blood after immunization, it is essential to make repeated tests at frequent intervals for some time afterward, at least for three weeks, not merely for one form of antibody or antibody action, but for all established forms — lysis, agglutination, opsonification, precipitation and complement-fixation. Judging from the statements in his articles, Besredka has made only occasional tests, mostly for agglutination, with negative results; but, as stated, that is not a sufficient basis on which to claim the existence of a new form of immunity.

AN INDEX TO THE CHEMICAL ACTION OF MICROORGANISMS ON THE NON-NITROGENOUS ORGANIC COMPOUNDS. By ELLIS I. FULMER, Professor of Biophysical Chemistry, and C. H. WERKMAN, Associate Professor of Bacteriology, assisted by ANELLA WIEBEN and CALVIN R. BREDEN, Instructors in Chemistry, Iowa State College. Cloth. Price, $4.50. Pp. 212. Springfield, Ill.: Charles C. Thomas, 1930.

This book consists of three tables and a list of approximately 500 references. The tables are substantially identical in content but different in arrangement. The items included are organisms, substrate, product and authority, the tables being keyed alphabetically to the first three items, respectively. Adequate cross-references are used for different names of the same organism.

The authors have confined this survey to "those instances in which a named organism acted on a named substance to produce a named compound." They state that they "have purposely omitted much material on the more common types of fermentation with only typical references, while for more uncommon types the treatment has been practically complete."

The user of the book, then, should expect to find every well established fermentation mentioned at least once. The reviewer used some of the fermentations with which he was most familiar as a basis for a critical examination.

In the section devoted to lactic acid as a product (pp. 145-151), *Streptococcus lactis* is mentioned once, as a fermenter of sucrose. *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* were not found here or elsewhere. One would gather (pp. 85-86) that lactose is fermented to lactic acid only by *Bacterium caucasicum, Bacillus coli, Lactobacillus leichmani, Amylobacter butylicus* and *B. tartricus.* On page 48, *Streptococcus lactis* is listed as fermenting dextrose and sucrose, no other sugar being mentioned.

Streptococcus paracitrovorus is mentioned as producing acetic and lactic acids from dextrose. *Streptococcus citrovorus* is not to be found. The action of these organisms on citric acid is not given.

B. welchii is listed as producing acrolein from glycerin. It is not mentioned in connection with the butyric fermentation.

The fermentation of galactose, sucrose, maltose and succinic acid to propionic acid by *Bacterium acidi-propionici d* is not mentioned.

In view of the omissions discovered in an examination that was far short of being exhaustive, it appears that this index, although undoubtedly very useful, fails to list completely either the well known or the less known proved fermentations. To the reviewer this seems a serious fault.

BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY. By DAVID H. BERGEY. Third edition. Cloth. Price, $6. Pp. 561. Baltimore: Williams & Wilkins Company, 1930.

This edition of Bergey's well known manual, sponsored by the Society of American Bacteriologists, contains 127 more pages than the second edition. It has most of the merits and the defects of its predecessors. It suffers from the uncritical acceptance of incomplete descriptions and from inaccuracies in recorded biologic characters and recognition marks. Curious lapses are frequent. To state that the habitat of *Clostridium tetani* is "the cause of tetanus" and the habitat of *Cl. botulinum* "the cause of botulism" is neither correct nor helpful. Especially does the manual lack authority from its failure to take into consideration numerous recent comprehensive studies in many groups. There is no evidence that Moltke's monograph on *Proteus vulgaris* was consulted in drawing up the list of characteristics of this organism. The genus *Salmonella* (paratyphoid bacilli), with which the reviewer is more or less familiar at the moment, is not handled in a way that inspires confidence in the general make-up of the book. Much space is wasted by unnecessary repetition. It is not clear why it should be thought necessary to state under each species of *Salmonella* that the rods are "gram-negative," since

the tribe *Bacterium*, under which *Salmonella* is placed, is characterized (p. 315) as consisting of "gram-negative rods." Dulcitol fermentation is employed as a differential character, although practically all recent observers agree in attaching little significance to the variations in fermenting this carbohydrate. The group is said (p. 339), quite correctly, to be characterized by inability to attack salicin, but *S. columbensis* (p. 346) is recorded as producing acid and gas in salicin. Six species of *Salmonella* enumerated by Castellani and Chalmers are included in the twenty species recognized by Bergey, although they have not yet been verified as true species by other workers on this group. *"S. typhimurium"* is classed (p. 395) as an independent species, but no one has yet shown that the cultures labeled by this name are any other than *S. aertrycke* or *S. enteritidis*. Basenau's *"B. morbificans-bovis,"* which is regarded as *Salmonella* by all recent investigators (e. g., White and Sladden and Scott), is placed in the genus *Flavobacterium* (p. 147). In a word, the descriptions, nomenclature and classificatory arrangement cannot be depended on as representing the best current opinion.

On the other hand, students of bacteriology have much to be grateful for to the author of this book. It is a good deal to have available a check list of generic and specific names under some sort of orderly arrrangement with references (which might be greatly and advantageously increased) to important classificatory sources. It is a book every bacteriologist must have access to, however much he may regret its shortcomings.

HUMAN BIOLOGY AND RACIAL WELFARE. Edited by EDMUND V. COWDRY, Professor of Cytology, Washington University, St. Louis, Mo. Price, $6. Pp. 612, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

According to the preface of the editor, the purpose of this book is to help break down the barriers separating the group of sciences that bear definitely on human welfare and which may be included under the collective term of "human biology." The book is intended principally for two groups of readers: for students, especially medical students, for whom it is essential to know as much as possible about human life in general, and for readers of more mature years who wish to look a little below the surface of things. The scope of the book is shown best by a brief summary of its contents. Edwin R. Embree, president of the Julius Rosenwald Fund, contributes an illuminating and comprehensive introduction. There are five parts: (1) Perspective: Life in space and time (H. N. Russell); (2) The Origin of Man: evolution traced biochemically (A. B. Macallum), the animal ancestry of man (William K. Gregory), the evolution of the brain (George H. Parker), mental evolution in the primates (R. M. Yerkes), societal evolution (W. M. Wheeler), human races (A. Hrdlička); (3) Man as a Physiological Unit: the vital units called cells (E. V. Cowdry), the relation of cells to one another (A. Carrell), the integrative action of the vascular system (W. B. Cannon), nervous integration in man (J. F. Fulton, C. S. Sherrington), the integration of the sexes (Clark Wissler); (4) Effects of Environment: the effect of climate and weather (E. Huntington), the reaction to food (E. V. McCollum), the influence of urban and rural environment (Haven Emerson, Earl B. Phelps), antisocial behavior (William Healey), adjustment to infectious diseases (H. Zinsser), what medicine has done and is doing for the race (H. Rolleston), the relation of science to industry (R. A. Millikan), the influence of education (John Dewey); (6) The Future: the inheritance of disease (Paul A. Lewis), some aspects of the biology of human populations (R. Pearl), the mingling of races (C. B. Davenport), the purposive improvement of the human race (E. G. Conklin), the intentional shaping of human opinion (H. A. Overstreet). This list contains many leaders in contemporary science, and obviously it is not possible to review in detail the chapters contributed by the individual authors. The topics have been well selected and assigned, and the book contains much important matter of wide interest.

Books Received

THE PRINCIPLES OF BACTERIOLOGY AND IMMUNITY. By W. W. C. Topley, M.A., M.D., M.S., F.R.C.P., Professor of Bacteriology and Immunology, University of London, Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine; and G. S. Wilson, M.D., M.R.C.P., D.P.H., Reader in Bacteriology and Immunology in the University of London, London School of Hygiene and Tropical Medicine. Two volumes. Price, $15. Pp. 1300. New York: William Wood & Company, 1929.

NINETEENTH ANNUAL REPORT OF THE STATE INSTITUTE FOR THE STUDY OF MALIGNANT DISEASES, Department of Health, State of New York. For 1929. Pp. 35. Albany, N. Y.: J. B. Lyon Company, 1930.

A HEALTH INVENTORY OF NEW YORK CITY. By Michael M. Davis and Mary C. Jarrett. Pp. 367. New York: Welfare Council, 1929.

MEDICAL EDUCATION AND RELATED PROBLEMS IN EUROPE. Commission on Medical Education (Willard C. Rappleye, Director of Study), New Haven, Conn., 1930.

METHODS AND PROBLEMS OF MEDICAL EDUCATION (Sixteenth Series). New York: The Rockefeller Foundation, 1930.

REFLEX ACTION: A STUDY IN THE HISTORY OF PHYSIOLOGICAL PSYCHOLOGY. By Franklin Fearing, Ph.D. Price, $6.50. Pp. 350, with illustrations. Baltimore: Williams & Wilkins Company, 1930.

THE CREED OF A BIOLOGIST: A BIOLOGIC PHILOSOPHY OF LIFE. By Aldred Scott Warthin, Ph.D., M.D., LL.D., Professor of Pathology, University of Michigan. Price, $1.50, cloth. Pp. 60. New York: Paul B. Hoeber, Inc., 1930.

IMMUNITY IN INFECTIOUS DISEASES: A SERIES OF STUDIES. By A. BESREDKA, Professor at the Pasteur Institute, Paris. Authorized translation by Herbert Child, M.R.C.S. (Eng.), L.S.A. Price, $5. Pp. 364. Baltimore: Williams & Wilkins Company, 1930.

AN INDEX TO THE CLINICAL ACTION OF MICROORGANISMS ON THE NON-NITROGENOUS ORGANIC COMPOUNDS. By Ellis I. Fulmer, Ph.D., Professor of Biophysical Chemistry; C. H. Werkman, Ph.D., Associate Professor of Bacteriology, assisted by Anella Wieben and Calvin R. Bieden, Instructors in Chemistry, Iowa State College. Price, $4.50, cloth. Pp. 212. Springfield, Ill.: Charles C. Thomas, 1930.

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